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Table of Contents

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ORIGINAL ARTICLES— Page

Constrictive Pericarditis, by M. J. Etheridge and J. D. Tange 121
Hyperparathyroidism, by Norman Wyndham 127
Enumeration and Sizing of Blood Cells by Means of Electrical Gating, by J. R. S. Douglas and Margaret E. Atkinson 130

REPORTS OF CASES—

Transition of Lymphatic Leukæmia to Reticulum Cell Sarcoma, by R. N. Ibbotson and C. W. Kingston 135
Idiopathic Hypercalcæmia of Infancy in Australia, by Ian S. Wallman 138
Retained Products of Conception, by Robert F. Zacharin 142

REVIEWS—

Growth Diagnosis 143
High Blood Pressure and Pregnancy 144

BOOKS RECEIVED 144

LEADING ARTICLES—

The Medical School of the University of New South Wales 145
Trachoma Virus 145

CURRENT COMMENT—

Monkey Malaria and Eradication Campaigns 146
The Surgical Approach to Advanced Cancer of the Breast 146
Medical School for Monash University 147

ABSTRACTS FROM MEDICAL LITERATURE—

Surgery 148

BRUSH UP YOUR MEDICINE—

The Nephrotic Syndrome 150

BRITISH MEDICAL ASSOCIATION—

New South Wales Branch: Scientific 151

OUT OF THE PAST 155

CORRESPONDENCE— Page

Institutional Neurosis and Aborigines 155
A Report on 500 Cases of Bleeding Peptic Ulcer Treated Medically with Minimal Transfusion of Blood 156
General Pharmaceutical Benefits 156
Differences in Axillary Temperature During Gall-Bladder Colic 157
Sales Promotion Methods 157
Preanæsthetic Sedation for Children 157
It Happened One Night 157

NOTES AND NEWS 157

MEDICAL PRACTICE—

National Health Act 159

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA 159

POST-GRADUATE WORK—

St. Vincent's Hospital, Sydney: Gastro-Enterology Unit 159
The Women's Hospital, Crown Street, Sydney 159

THE WORLD MEDICAL ASSOCIATION 159

AUSTRALIAN MEDICAL BOARD PROCEEDINGS—

New South Wales 160

NOTICE—

The Children's Medical Research Foundation of N.S.W. 160

NOMINATIONS AND ELECTIONS 160

DIARY FOR THE MONTH 160

MEDICAL APPOINTMENTS: IMPORTANT NOTICE .. 160

EDITORIAL NOTICES 160

CONSTRICTIVE PERICARDITIS.

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CONSTRICTIVE PERICARDITIS is an uncommon condition, and probably at the most only two or three patients with this condition are admitted to a major hospital in Australia in any one year. The disease has been studied extensively in other countries. Dalton, Pearson and White (1956) reported a group of 78 cases. The study and follow-up of these patients have continued since the first review by White (1935). Other large series include those by Chambliss, Jaruszewski, Brofman, Martin and Feil (1951), by Evans and Jackson (1952), by Burwell (1957) and by Gimlette (1959).

The published descriptions of constrictive pericarditis in Australia have so far been limited to a small number of separate case reports (Anderson, 1945; Stuckey and Epps, 1957; Monk, 1957; Rowe, 1959). The clinical features of the earlier cases in the present Royal Melbourne Hospital series formed the basis of a previous paper on this subject by one of us (Etheridge, 1955). An increased awareness of the clinical pattern of this disease should lead to earlier diagnosis and more prompt surgical treatment. The present paper describes the clinical features and results of operation in 14 patients admitted to the Royal Melbourne Hospital since 1948.

Material.

The 14 patients were aged from 17 to 64 years when they first presented at the Royal Melbourne Hospital (Table I). This illustrates not only the wide range of age presentation, but also the fact that there is no special age incidence. There were nine males and five females. A preponderance of males over females has been noted previously. Dalton *et alii* (1957) encountered 59 males in their series of 78 cases. Two patients, aged 22 and 26 years respectively, presented an acute course with the signs of pericardial constriction developing during recovery from acute tuberculous pericarditis.

The diagnosis was confirmed at operation in 12 cases. Of the two patients who did not come to operation, one was a man, aged 64 years, who had minimal symptoms and signs of constriction; the other was a man, aged 45 years, who was a chronic alcoholic, and he was considered unsuitable for operation.

TABLE I.

Clinical Features in Constrictive Pericarditis.

Case Number and Patient's Sex and Age (Years).	Symptoms.					Signs.										X-Ray Findings.	
	Duration.	Effort Dyspnœa.	Orthopnœa.	Chest Pain.	Cough.	Œdema.	Blood Pressure. (Min. of Mercury.)	Rhythm.[1]	Pulse.[1]	Raised Jugular Venous Pressure.	Auscultation.[1]	Chest.	Liver Palpable.	Ascites.	Spleen Palpable.	Heart Size.[1]	Pericardial Calcification.
I : M. : 59	2 months.	+	0	0	0	+	100/110	S.R.	N.	+++	T.R.	Clear.	+++	0	0	N.	+
II : M. : 55	4 months.	0	0	0	+	+	110/85	S.R.	P.P.	+++	D.R.	Râles.	+++	+	+	N.	0
III : F. : 17	9 months.	+	0	0	0	+	125/80	S.R.	P.P.	++	T.R.	Effusion.	++++	0	0	N.	+
IV : F. : 40	5 years.	+	0	0	+	+	115/65	A.F.	Full.	++	T.R.	Râles.	+++	+	+	+	0
V : M. : 31	8 months.	+	0	+	+	+	125/90	A.F.	P.P.	+	M.S.M. T.R.	Râles.	++	0	0	+	+
VI : F. : 22	2 months.	+	0	0	0	0	105/70	S.R.	Small.	++	P.F.R.	Effusions.	+++	0	+	P.E.	0
VII : M. : 49	5 years.	+	+	+	+	+	120/70	A.F.	Small.	+	T.R.	Râles.	+++	+	0	+	+
VIII : M. : 27	4 months.	+	0	0	0	0	105/60	S.R.	Small.	++	P.F.R.	Effusions.	++	0	+	P.E.	0
IX : M. : 64	3 months.	+	0	0	0	+	130/80	A.F.	N.	+	D.R.	Clear.	++	0	0	N.	+
X : M. : 22	5 years.	+	0	+	+	+	120/90	A.F.	N.	++	T.R.	Effusion.	+++	+	+	+	0
XI : M. : 49	1 year.	+	+	0	0	+	100/115	A.F.	P.P.	++	T.R.	Clear.	+++	0	+	+	0
XII : F. : 48	3 years.	+	+	0	0	+	110/80	S.R.	Small.	+++	T.R.	Effusion.	+++	+	0	N.	0
XIII : F. : 30	2 years.	+	0	0	0	+	100/65	S.R.	Small.	+++	T.R.	Effusion.	++	+	+	N.	+
XIV : M. : 40	2 months.	+	0	0	0	+	130/90	S.R.	Small.	++	T.R.	Clear.	+++	0	0	N.	+

[1] N., normal; D.R., dual rhythm; T.R., triple rhythm; S.R., sinus rhythm; A.F., auricular fibrillation; P.P., pulsus paradoxus; M.S.M., mitral systolic murmur; P.F.R., pericardial friction rub; P.E., pericardial effusion.

Careful inquiry into the past history of the patients with chronic constriction did not reveal evidence of previous tuberculous infection.

Symptoms.

The principal symptoms of pericardial constriction are dyspnœa on effort, swelling of the abdomen, œdema of the legs and swelling of the face. Other symptoms consist of undue fatigue, epigastric discomfort and coldness of the extremities, and occasionally syncope may follow exertion. The onset of symptoms is usually gradual; rarely, it is sudden, and then may be due to the occurrence of auricular fibrillation (Andrews, Pickering and Sellors, 1948).

Effort dyspnœa in these patients is generally not so troublesome as in congestive cardiac failure, and relief is usually obtained more readily with rest. Evans and Jackson (1952) emphasized this feature, and they suggested that the term "restricted ambulation" should be used rather than effort dyspnœa. However, occasionally effort dyspnœa is pronounced and may be associated with orthopnœa.

Swelling of the abdomen with or without ascites is a prominent early symptom. It commonly precedes peripheral œdema, and it is usually out of all proportion to the degree of shortness of breath when compared with similar degrees seen in patients with congestive cardiac failure. Swelling of the face may be present for a considerable time before other symptoms appear. It may be associated with a sensation of fullness in the head and neck, particularly on stooping.

All but one of our patients complained of effort dyspnœa. The exception (Case II), a male, aged 55 years, had noted swelling of his face, ankles and abdomen during the previous four months; but he had denied shortness of breath on ordinary degrees of exertion.

Orthopnœa and paroxysmal dyspnœa were never conspicuous features in the patients with chronic constriction, and there were only three who admitted to several episodes of orthopnœa. A sensation of fullness in the neck and epigastric discomfort was occasionally described, and about half the patients had a history of chronic cough with varying amounts of sputum. The duration of symptoms in the patients with chronic constriction varied from two months to five years prior to their first admission to hospital or before the diagnosis was made, and in five of these patients some evidence of constriction had been present for at least two years.

Signs.

All our clinical patients had an elevated jugular venous pressure, enlargement of the liver and a small pulse with a normal or low blood pressure. Most had dependent œdema and triple rhythm. Pulsus paradoxus and inspiratory filling of the cervical veins could be demonstrated in some patients. Auricular fibrillation was present in six patients, whose ages ranged from 22 to 64 years.

The cardiac impulse was faintly palpable in 10 cases; in one the apex beat was regarded as forceful, and in the remaining three it could not be felt. Cardiac enlargement as judged by the site of the apex beat was present in two cases. In six cases the spleen was enlarged and palpable at the left costal margin. This is a higher incidence of splenic enlargement than has been noted in most of the other reported series.

Although the widespread crepitations of pulmonary congestion were not encountered, practically all patients had some adventitial sounds, such as basal râles and scattered rhonchi, and a pleural effusion was present in six cases. In two of these, aspiration of the effusion was necessary.

Radiological Findings.

The radiological signs include a cardiac silhouette of normal or slightly increased size with diminished amplitude of pulsation, a convex right border from diaphragm to aorta, a prominent superior vena caval shadow, pulmonary vascular shadows which are normal or show only slight congestion, and pericardial calcification. The last of these is the most valuable radiological sign. In those instances in which the calcification comprises but a thin line, its recognition requires careful inspection of a suitably exposed X-ray film. Pericardial calcification must be differentiated from calcification in an old infarct or old thrombus, and from ring calcification of the left atrium. The sites of preference for pericardial calcification are the coronary sulcus, the diaphragmatic surface, and the sternal aspect of the right ventricular area and along the left border of the heart. Calcification is rarely encountered over the left atrium in this condition (Kerley, 1948). Plum, Bruwer and Clagett (1957) did not find radiological evidence of pericardial calcification over the left atrium in any of their 35 cases.

Evans and Jackson (1952) noted backward displacement of the œsophageal stream in 21 of their 30 cases. They differentiated the œsophogram of constrictive pericarditis from that of mitral stenosis by the presence of a relatively clear area between the œsophagus and the denser part of the heart shadow, whereas in mitral stenosis these two structures are usually contiguous. Their explanation of this difference is that, in constrictive pericarditis, the œsophagus is displaced by an undistended left atrium. However, other writers, who have commented on this simulation of mitral stenosis, have reported cases of con-

strictive pericarditis in which a greatly enlarged left atrium was found at operation (Burwell, 1951; McKusick, 1952). White *et alii* (1948) stated that left ventricular constriction or calcification in the atrio-ventricular groove between the left atrium and ventricle might cause left atrial enlargement similar to that seen in mitral stenosis.

In our cases, the cardiac silhouette was slightly to moderately enlarged in five, considerably enlarged in one (Case V) and normal in size in the remainder. The amplitude of pulsation was diminished in all but one. A convex right border in the antero-posterior view was almost a constant feature, and pericardial calcification (Figure I)[1] was visible in seven cases. In two the left atrium was enlarged, and the backward displacement of the barium-filled œsophagus could not be clearly distinguished from that seen in mitral stenosis. In all except two cases the lung fields were free from significant congestion.

As was noted above, the patient in Case V, a male, aged 31 years, was of particular interest, because of the finding of considerable cardiac enlargement. He was admitted to the hospital on June 2, 1952, with a history of effort dyspnœa during the preceding eight months. He had had a productive cough for six months, and his ankles had been swollen for three months. At the age of 15 years he had suffered from a rheumatic condition. There was no history of tuberculosis. His blood pressure was 125/90 mm. of mercury, his pulse was irregular owing to auricular fibrillation, and the jugular venous pressure was slightly elevated. The apex beat was impalpable, and a loud, blowing, apical systolic murmur was noted. Scattered rhonchi were present in both lungs, and there were numerous basal crepitations. The liver was palpable 3 cm. below the costal margin. X-ray examination showed definite cardiac enlargement with enlargement of the left atrium, and in the lateral views a ring of calcified pericardium was visible (Figure II (*a*)). The electrocardiogram showed auricular fibrillation, left axis deviation and low biphasic *T* waves.

Thoracotomy was performed on June 20, 1952. The heart was constricted by a tough fibrous parietal pericardium, with calcification posteriorly and around the atrio-ventricular sulcus. A systolic thrill was palpable over the enlarged left atrium. Excision of the thickened pericardium was incomplete because of inadequate exposure through the thoracotomy incision. Microscopic examination of the excised pericardium showed avascular, acellular fibrous tissue. After this operation his symptoms persisted, and his heart became larger. Operation was again undertaken on December 8, 1954, and the remaining portion of the thickened pericardium was removed. When he was last seen in 1955, he had persistent congestive cardiac failure with mitral valve incompetence and gross cardiac enlargement (Figure II (*b*)). In this case, constrictive pericarditis was associated with an incompetent mitral valve. The latter condition was probably of rheumatic origin. It is reasonable to suppose that cardiac enlargement was due to mitral regurgitation, and this enlargement was present before the development of constrictive pericarditis. Removal of the constricting and unyielding pericardium was followed by further cardiac enlargement. It is possible that the association of constrictive pericarditis and mitral valve disease in this case was not fortuitous, but that both conditions were a sequel of rheumatic fever.

The Electrocardiogram.

The most constant feature of the electrocardiogram of constrictive pericarditis consists of biphasic or sharply inverted *T* waves, with little or no *S-T* segment displacement. The deformity of the *T* waves is seen in the standard leads and most of the precordial leads. Dalton *et alii* (1948) found *T* wave abnormalities in all their 77 cases in which electrocardiograms were available. The amplitude of the *QRS* complex is inclined to be low, though it is rarely less than 5 mm.

Evans and Jackson (1952) have emphasized the occasional appearance of a notched or step-like *P* wave, and Chambliss *et alii* (1951) noted broad and notched *P* waves in 20 of their 61 cases. This type of wave is similar to the dominant left atrial wave of mitral stenosis. Brigden (1957) noted four instances of a left atrial *P* wave in his 50 cases of cardiomyopathy. There does not appear to be a simple relation between this wave and the degree or presence of left atrial enlargement in constrictive pericarditis.

Characteristic *T* wave changes were present in the electrocardiogram of all our patients (Figure III), and the amplitude of the *QRS* complex was usually low. In four tracings there was a notched or step-like *P* wave (Figure IV).

Laboratory Investigations.

Laboratory investigations add but little to the diagnosis of constrictive pericarditis. In certain cases the plasma protein content is reduced, and in one report (McKusick, 1952) this reduction was found in cases in which the disease was of long duration. Liver damage is found in a high proportion of patients coming to autopsy (Paul, Castleman and White, 1943; Chambliss *et alii*, 1951). Tissue obtained by liver biopsy may therefore be useful in assessing prognosis.

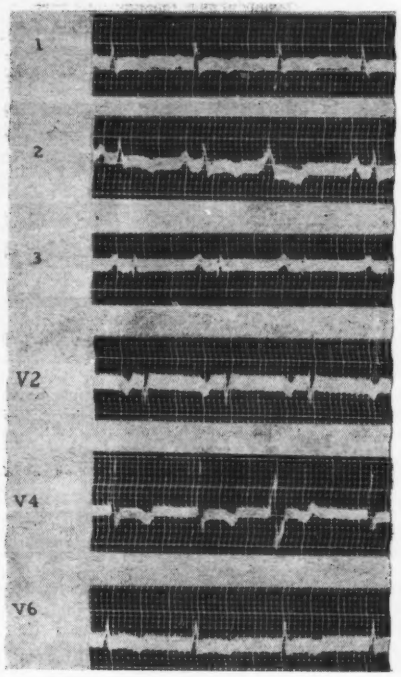

FIGURE III.
Electrocardiogram showing inversion of the *T* waves.

In this group of 14 cases only limited laboratory data were available. The Mantoux test produced a positive reaction in seven of the ten cases in which the test was performed. The plasma protein levels were usually slightly reduced, and the average total plasma protein level was 5·7 grammes per 100 ml. The serum bilirubin level was frequently slightly raised, and it was common to find a level of 1 to 3 mg. per 100 ml.

Liver biopsy was performed in five cases. Cirrhosis of varying degree was found in three. Two of these patients had complained of their symptoms for five years, and they showed the most advanced changes in liver architecture with the histological features of portal cirrhosis. In one of the remaining two cases the histological findings in the liver were normal and in the other there was hepatic congestion.

Cardiac Catheterization.

Hansen, Eskildsen and Götzsche (1951) and McKusick (1952) have described the pressure curves obtained by

[1] For figures I, II (*a*), II (*b*), VII (*a*) and VII (*b*) see art-paper supplement.

cardiac catheterization of patients with constrictive pericarditis.

Scannell, Myers and Friedlich (1952) reported the pre-operative and post-operative cardiac catheterization findings in five cases and pointed out the large element of left-sided constriction present in some of these cases.

Cardiac catheterization was performed in two of our cases, and the pressure curves obtained conform to the patterns described by other writers. The pulmonary vascular pressures and the right ventricular pressure were raised. The right ventricular pressure curve showed the characteristic early diastolic fall, followed by a sharp rise which continued as a plateau to the end of diastole. The

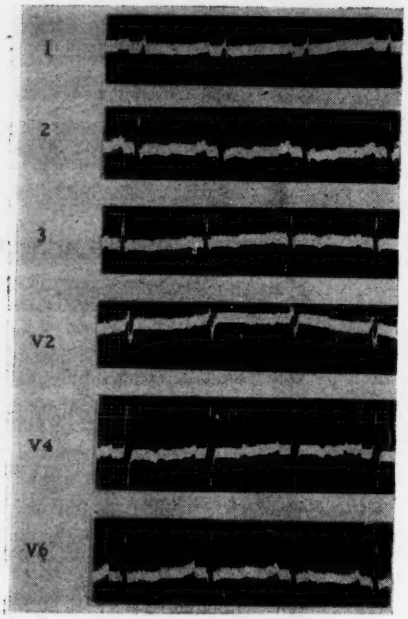

FIGURE IV.
Electrocardiogram showing notched, step-like *P* waves.

right atrial pressure was elevated and the pulse pressure increased (Figure V).

The absence of any significant gradient between superior vena caval and right atrial pressures shows that constriction of the great veins by scar tissue is not an important factor in the production of symptoms.

Cardiac catheterization was performed on another patient not included in the present series, who had extensive pericardial calcification, without either symptoms or signs of constriction. There was no pulmonary hypertension, and the right ventricular and right atrial pressures were normal. However, the right ventricular pressure curve showed a slight fall in the early part of diastole (Figure VI—Patient W.). This patient remains under regular observation.

Operation Findings and Results.

Most patients who survive operation show considerable improvement and are able to work (Burwell, 1957). Good results were reported by Dalton *et alii* (1956) in two-thirds of the patients submitted to surgery, although the first patient in their series was operated upon in 1928. Operation was performed on 12 of our patients, and in eight a good result was obtained. These included the two patients with tuberculous pericarditis.

In Case VI, the patient, a female, aged 22 years, presented in January, 1951, with a massive pericardial effusion and bilateral pleural effusions. Tubercle bacilli were isolated from the pericardial fluid. She was treated with streptomycin and PAS. Signs of constriction appeared in April, and pericardial resection was carried out in June, 1951. Caseating tuberculous granulation tissue was found at operation. Pericardial resection was successful, and she has obtained an excellent result. X-ray films of her chest today show normal lung fields, and the cardiac silhouette is of normal size and contour (Figures VII (*a*) and (*b*)).

In Case VIII, the patient was a Swedish seaman, aged 20 years; he was admitted to hospital on October 21, 1951. During the previous two weeks he had suffered from malaise and fever. His blood pressure was 105/60 mm. of mercury, and the pulse was regular. The venous pressure was not elevated, the apex beat was palpable and there was a loud pericardial friction rub. The liver was slightly enlarged, and the spleen was palpable. X-ray examination showed an enlarged and globular cardiac outline. The electrocardiogram showed low inverted *T* waves. At the end of the first month the friction rub disappeared and a triple cardiac rhythm with some elevation of the venous pressure were first noted. During the next few months there was progressive enlargement of the liver, with further increase in the jugular venous pressure. Bilateral pleural effusions developed, and the serum bilirubin level rose to 8 units. Liver biopsy revealed normal liver architecture, with infiltration of the portal tracts by round cells and occasional polymorphs. Throughout this period the patient had an intermittent fever, despite therapy with streptomycin and PAS.

At operation on March 14, 1952, the pleural sacs were found to be adherent to the pericardium, both layers of which were thickened. The parietal and visceral layers were easily separated, but the latter was closely adherent to the myocardium and impeded diastolic filling. The visceral layer was either removed or incised so that the heart's action was unimpaired. Microscopic examination of the excised pericardium showed fibrous tissue and tubercles with caseation. Tubercle bacilli could not be grown on culture from the excised tissue. Chemotherapy was continued during convalescence, the jugular venous pressure fell to normal and the pleural effusions resolved. A chest X-ray film in June, 1952, was of normal appearance, and in February, 1955, the patient's doctor in Sweden reported that he had completely recovered.

It is noteworthy that in these two cases, in which constriction developed within a few months of the onset of acute tuberculous pericarditis, resection of the tuberculous pericardium was not followed by spread of the disease into surrounding tissues. Both patients have made a complete recovery.

In four cases an unsatisfactory result was obtained. In one (Case II) operation was abandoned, because the pericardium and epicardium were in one tough layer which involved the main coronary arteries and a plane of cleavage could not be obtained. The second case was that of the patient who had considerable cardiac enlargement with mitral incompetence as well as constrictive pericarditis.

The third patient was a man, aged 49 years. Pericardial constriction had been present for several years. A ring of calcium encircled both ventricles, and although bone forceps were needed, fairly complete removal was obtained. Some improvement followed his operation, which was performed in 1951; but his venous pressure remained elevated, and he still requires medical treatment to control œdema.

The other patient, a man, aged 22 years, had suffered from dependent œdema and exertional dyspnœa for five years. Liver biopsy revealed active fibrous-tissue proliferation encircling the liver lobules; there was distortion of the portal veins, but no active destruction of liver tissue was apparent. Removal of the thickened and constricting pericardium was fairly complete. A stormy convalescence was complicated by œdema, ascites and an empyema. When he was reviewed 18 months after operation, he was able to work; but auricular fibrillation had persisted, his liver was enlarged and diuretics were needed to check recurrent œdema. Clubbing of the fingers had developed and the empyema sinus was draining pus.

Discussion.

Most of the available evidence supports the contention that constrictive pericarditis is the result of a previous tuberculous infection, but in relatively few cases is this definitely demonstrable. Paul *et alii* (1948) found nine

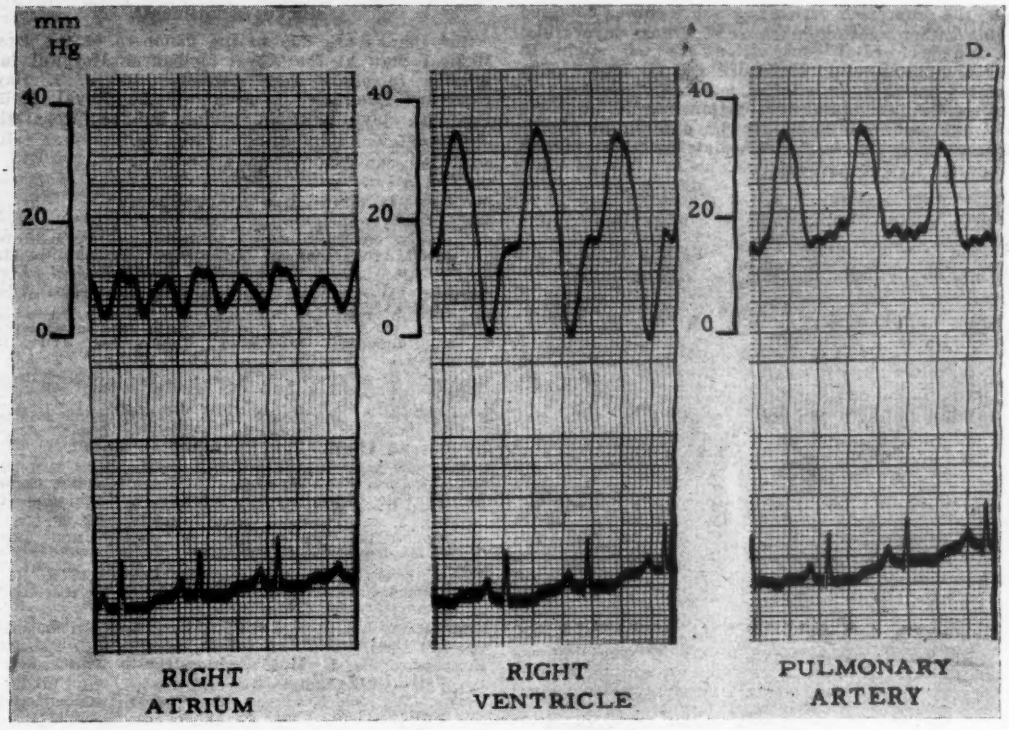

FIGURE V.

Tracing obtained by cardiac catheterization, showing raised right atrial and pulmonary artery pressures (Case XII). The right ventricular pressure curve shows a characteristic early diastolic fall followed by a sharp rise, which continues as a plateau to the end of diastole.

proven cases of tuberculosis in their 53 patients, and Chambliss *et alii* (1951) 16 cases in 61 patients. The only certain evidence of a tuberculous ætiology is the isolation of the tubercule bacillus or the presence of characteristic granulation tissue. This evidence is usually obtained in those patients who develop constriction soon after acute pericarditis, but rarely in patients with chronic constrictive pericarditis. In the chronic cases the histology is that of non-specific, dense fibrous tissue. However, the finding of non-specific scar tissue is not evidence against a tuberculous origin. McKusick (1952) cites a patient with proven tuberculous pericardial effusion who finally developed chronic constriction; at operation only non-specific, hyalinized and calcified pericardial scar was demonstrated. Andrews, Pickering and Sellors (1948), from a study of the after-history of patients with tuberculous and septic pericarditis, concluded that tuberculosis was the chief cause in Great Britain. In our cases tuberculosis was proven only in the two instances in which constriction followed soon after acute pericarditis. Rarely, constrictive pericarditis follows hæmopericardium. Ehrenhaft and Taber (1952) cited six cases in which constriction had followed hæmopericardium, and added one case of their own. In countries where amœbiasis is endemic, constrictive pericarditis may follow the rupture of an hepatic abscess into the pericardium (Lamont and Pooler, 1958).

The essential pathological change is the transformation of the pericardium, usually in its whole extent, into a tough fibrous membrane, which may be up to 2 cm. in thickness. It is closely adherent to the myocardium and occasionally invades it. Often the fibrous tissue extends into the mediastinal structures and the adjacent pleura. Calcification, though often conspicuous, is not an essential feature. The ventricular muscle may be thinned and the right ventricle may be perforated during the decortication. Histological studies indicate that atrophy of the myocardium develops early in the disease, and that it is not progressive (Dines, Edwards and Burchell, 1958). Atrophy of the myocardium has also been observed in animals in which constriction is produced experimentally (Roberts and Beck, 1941). These authors consider the phenomenon to be a consequence of disuse atrophy, and suggest that slow recovery after decortication may be related to this factor.

In cases in which symptoms have been present for years, the combination of low cardiac output and prolonged passive venous congestion is responsible for the high incidence of hepatic fibrosis (Sherlock, 1951). In one series of 18 patients with fibrosis of the liver due to cardiac disease, 5 suffered from constrictive pericarditis (Koletsky and Barnebee, 1944). Chambliss *et alii* (1951) reviewed the autopsy findings on 16 patients with constrictive pericarditis; 2 had cirrhosis, and in a further 7 there was liver-cell damage with conective-tissue and bile-duct proliferation. Paul *et alii* (1948) found cirrhosis of the liver in 14 of their 16 patients who came to autopsy.

The differential diagnosis of constrictive pericarditis can, at times, be extremely difficult, especially when calcification is absent. Two patients, who were encountered during the period of this study and are not included in the present series, underwent thoracotomy because their clinical features, except for heart size, were consistent with constrictive pericarditis; but both were found to have a dilated heart and a thickened pericardium without constriction. A third patient displayed features indistinguishable from those of constrictive pericarditis, and autopsy revealed constrictive endocarditis.

Diffuse myocardial fibrosis without pericardial abnormality may produce all the clinical manifestations of constrictive pericarditis (Burwell and Robin, 1954).

Moreover, the differences between pressure curves obtained by cardiac catheterization in cases of diffuse myocardial fibrosis and pericardial constriction are too slight to have any diagnostic value. McKusick and Cochran (1952) have pointed out that the clinical features of constrictive endocarditis and pericardial constriction may be identical, and that the two conditions can be differentiated only by thoracotomy or by intrapericardial injections of air.

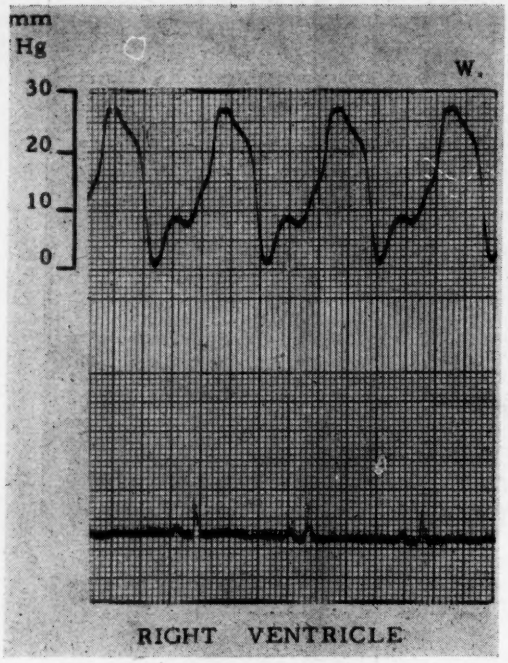

FIGURE VI.

Tracing obtained by cardiac catheterization of a patient (W.), who had pericardial calcification, but did not have the symptoms and signs of constriction. The right ventricular pressure curve shows a slight fall in the early part of the diastole.

Thus there remains a small residue of cases in which exploratory thoracotomy is necessary before the diagnosis is certain. Exploration is justified in these cases to ensure that they are not denied the benefit of surgical relief of constriction.

Summary.

The clinical features of constrictive pericarditis have been studied in 9 male and 5 female patients.

Limitation of effort tolerance, a small pulse, raised jugular venous pressure, œdema and liver enlargement were the commonest manifestations; pulsus paradoxus, ascites and splenomegaly were less frequent. A third heart sound was usually audible, and the heart shadow was small or only moderately enlarged. Pericardial calcification was present in half the patients.

The clinical picture can be closely simulated by that of severe myocardial fibrosis and of constrictive endocarditis, and thoracotomy may be required for diagnosis.

Two patients developed constriction after tuberculous pericarditis; in the remainder no cause could be demonstrated.

Operative cure was attempted on 12 patients; 8 are now able to lead normal lives. Failures were attributable to myocardial fibrosis, cirrhosis of the liver, coincidental mitral valve disease, and technical difficulties in resecting the pericardium.

Acknowledgements.

Our thanks are due to the members of the Honorary Medical Staff at the Royal Melbourne Hospital for permission to study their patients. Mr. J. I. Hayward, Honorary Thoracic Surgeon at the Royal Melbourne Hospital, gave valuable advice in the preparation of this paper.

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HYPERPARATHYROIDISM.[1]

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THERE may be many people with hyperparathyroidism in this community — people with renal calculi in whom disturbance of calcium metabolism has not been demonstrated. The activities of the Clinical Research Unit of the Royal Prince Alfred Hospital brought to light at least half the cases mentioned in this paper and carried out the detailed investigation in most of the others. In the hope of stimulating further interest in this disease, the subject is reviewed in the light of eleven patients who have come under our surgical care. Naturally the surgical aspects are stressed. A discussion of the finer biochemical details would be presumptuous.

Comparative Anatomy.

Cyclostomes possess seven pairs of parathyroid glands, corresponding to their gill pouches; but in amphibia and all higher forms of chordates these are reduced to two pairs, corresponding to the third and fourth pharyngeal pouches. One might postulate, unscientifically, that fishes consume so much vitamin D that they do not need parathyroid glands. It is curious that, so far, they have not been found in the whale embryo.

Some animals possess accessory parathyroid tissue in addition to the usual two pairs of glands, so that total extirpation may be difficult. Some breeds of dog show no change in calcium level in the blood after removal of thyroid, thymus and parathyroid glands; 50% of cats appear to have parathyroid tissue in the thymus. Brewer (1934) has shown that this may be so in some humans. In many rats only two parathyroid glands exist, and these may be buried in the thyroid.

Histological Considerations.

In most animals, and in man until puberty, the parathyroid gland is composed of "chief" cells, which have a clearly demarcated nucleus in a faintly acidophilic, almost clear cytoplasm. Towards middle life colloidal material may be seen between the cells. Fat cells appear in the stroma. Other parenchymal cells are often seen, namely oxyphil cells, which appear at puberty, and "water clear" cells. The former are larger than the chief cells, and their cytoplasm contains granules which fill the cell and stain to a varying degree, so that pale oxyphil and dark oxyphil cells are described by Castleman and Mallory (1935). In our small number of cases, the depth of staining appeared to be of no functional significance. In parathyroid hyperplasia the "water clear" cells often form the bulk of the gland. These cells are much larger than the chief cells, and have a thin but very clear cell outline and a cytoplasm which is devoid of any stainable material. In one case hyperplasia occurred in the chief cells.

CASE I.—A man, aged 33 years, was admitted to hospital for pyelolithotomy. Symptoms had begun in 1950, when he had polyuria. Four years later, hæmaturia and renal colic led to the discovery of two renal calculi in the left kidney. After these had been removed at operation, the patient's serum calcium level was 12·8 mg. per 100 ml. and his serum phosphorus content 3·2 mg. per 100 ml. There were no skeletal defects visible on X-ray examination. A Sulkowitch test gave strongly positive results. The results of six days on a diet low in calcium and phosphorus are shown in Table I.

Many other confirmatory investigations were carried out.

At operation on December 13, 1957, the right superior parathyroid gland was found to be enlarged, the left inferior parathyroid gland was not identified with certainty, and the other two glands were normal. The enlarged gland, but no other parathyroid tissue, was removed. The calcium and phosphorus levels after operation were as shown in Table II.

The parathyroid gland removed was 1·3 cm. in length. It did not contain an adenoma, but was composed almost entirely of chief cells with some acinar formation. The patient had no further trouble.

[1] Based on a paper given at a surgical seminar at Royal Prince Alfred Hospital, Sydney.

Several of the adenomata removed contained all four types of cell and we regard them as different phases in the activity of the one cell.

We were asked to examine one patient with parathyroid carcinoma, showing signs of hyperparathyroidism. Albright (1948) stated that only three such cases had been reported up till 1942. This patient was transferred from another hospital, and the case has been reported elsewhere. It is not included in this series.

TABLE I.

Substance.	Intake. (Milligrammes.)	Output. (Milligrammes.)	Urinary Calcium Excretion. (Milligrammes per Day.)	Stool Calcium Excretion. (Milligrammes per Day.)	Balance. (Milligrammes per Day.)
Calcium ..	212	369	289	80	−157
Phosphorus ..	778	1104	899	205	−326

Gross Anatomy.

Normally the parathyroid glands are flattened with a sharp border, and measure 3 to 6 mm. in length, 2 to 4 mm. in width and 0·5 to 2 mm. in thickness. The upper pair lies medial to the upper pole of the thyroid gland, and the lower pair lies under cover of the lobe of the thyroid gland, near where the main branches of the inferior thyroid artery penetrate the fascia of the thyroid. These glands are slightly darker than the surrounding fat or neighbouring lymph nodes, and are reached respectively by a superior and an inferior branch from the thyroid artery.

TABLE II.

Date.	Calcium. (Milligrammes per 100 ml.)	Phosphorus. (Milligrammes per 100 ml.)
December 13 (p.m.) ..	10·4	4·3
December 14	9·6	2·2
December 16	9·2	4·3
December 19	9·2	3·3
January 2	10·5	3·8
February 11	10·5	2·7

This description applies to the majority of cases seen during dissection of the neck during thyroidectomy or parathyroidectomy. However, every surgeon with experience in this field admits difficulties, and many speak about biopsies and frozen section examination to determine the nature of the tissue seen. In one case I removed what were thought to be two identical lymph nodes, since they were rounded and had no obvious arterial twig entering them. One, taken from the mediastinum, proved to be an enlarged parathyroid gland, and the other a lymph node. Even in the quiet serenity of the autopsy room, pathologists have often failed to demonstrate two pairs of glands. This difficulty in recognition applies especially to the normal gland. Enlarged hyperplastic glands and, even more, adenomatous glands, are much easier to find and to recognize. We had seven such cases. Yet even these may elude the surgeon. We failed in one case to find the abnormal gland after the neck exploration. The mediastinal exploration was done by Cope, of Boston, who removed an adenoma from the posterior mediastinum. In another case we have identified three normal glands, but were unable to demonstrate the abnormal one.

CASE II.—A male patient, aged 41 years, was admitted to hospital on July 6, 1955, with renal calculi and for a detailed study of his calcium metabolism prior to operation for hyperparathyroidism. Immediately before operation his serum calcium level was 12·9 mg. per 100 ml. and his serum phosphorus level 2·63 mg. per 100 ml. The serum alkaline phosphatase level was then 11·8 King-Armstrong units. There was no demonstrable skeletal decalcification. At operation, on July 14, three parathyroid glands were found.

but not the left inferior. Mediastinal exploration was carried out at the same time as the neck dissection. The right inferior parathyroid gland was enlarged and was removed. It was composed of oxyphil cells. The left recurrent laryngeal nerve was damaged during the procedure, but appeared to recover some weeks later. The patient's post-operative course was stormy, owing to infection of the sternum at the operation site. Operation had to be performed for this two months later. His calcium metabolism was unaltered by the operation.

Once the diagnosis of hyperparathyroidism has been made, it is up to the surgeon to produce results. As Cope (1936) said, there is no place for "exploratory operation". When no tumour is found, the position is still that the tumour exists. Nor should exploration cease with the discovery of one adenoma. Multiple tumours sometimes occur, and it is said that more than four glands may exist.

A hyperactive adenoma is often rounded. It may vary in colour from cream through brown and red to blue. It may resemble to a slight extent a small thyroid nodule. Several adenomata were 2 cm. in diameter. In one case two such adenomata were removed, and four years later a third adenoma was removed.

CASE III.—A woman, aged 51 years, was admitted to hospital in October, 1953, with a history of urinary symptoms since 1945. In 1947 a right nephrectomy for hydronephrosis and renal calculi had been performed. On September 30, 1953, examination of the blood showed the patient's serum calcium level to be 15·9 mg. per 100 ml., the phosphorus level 1·96 mg. per 100 ml., the total protein content 6·7 grammes per 100 ml., and the alkaline serum phosphatase level 10·1 King-Armstrong units. There was no evidence of changes in the bones, but there were a few calcareous deposits beneath the conjunctivæ.

At operation, on October 29, two parathyroid adenomata were found, one in the right superior and one in the left inferior position. The patient was given calcium as a routine after operation. Her blood biochemistry returned immediately to normal and remained so, and at no time did she show any evidence of tetany.

Four years later, recurrence of symptoms and abnormal biochemical findings led to the removal of a third adenoma.

In another case, two hypertrophied glands were found and removed, with subsequent return to biochemical and clinical normality. In one instance of parathyroid hyperplasia, biopsy of a small lymph node revealed unsuspected Boeck's sarcoid.

Diagnosis.

In actual practice, the diagnosis in most cases depends upon the physician and biochemist. Some 20% of patients have skeletal changes rendering diagnosis by the radiologist possible. Much depends upon the careful and repeated examination and investigation of all cases of renal calculus.

From 1928 until 1942, only 14 cases were found at the Mayo Clinic; but in the next 13 years, after Albright's teaching, 193 additional cases were found (Black and Zimmer, 1955). In our small series, half the patients had skeletal involvment, including fracture of the femur. Three had renal calculi without obvious decalcification of the bones. It is hard to escape the conclusion that undiagnosed cases of hyperparathyroidism exist in the community. One normal figure for serum calcium and phosphorus levels is not sufficient to exclude the diagnosis. Sometimes years of suggestive symptoms may exist before appropriate investigations are begun.

CASE IV.—A woman, aged 52 years, was admitted to hospital on March 23, 1955. She had three children, aged 20, 19 and 13 years, and during each pregnancy she had been troubled by nausea and vomiting, which were treated successfully by the administration of calcium. She gave a history of renal calculi for nine years, and in 1954 had passed a stone. Examination of the blood gave the following results: serum calcium level, 12·7 mg. per 100 ml.; serum phosphorus level, 3·0 mg. per 100 ml.; serum alkaline phosphatase level, 23·1 King-Armstrong units. She had no polyuria and no desire for milk foods, her appetite was good, and she was taking no alkalis or calcium. X-ray examination showed no evidence of skeletal decalcification. At operation on March 10, an adenoma of the left inferior parathyroid gland measuring 2 cm. by 1 cm. by 0·5 cm. was removed. Microscopic examination showed it to be composed of pale oxyphil cells. Immediately after operation the patient's blood biochemistry returned to normal.

In the present series, symptoms varied so much from patient to patient that it is clear that careful biochemical investigation is the only way of picking up borderline cases. The renal symptoms due to stone or to impaired function, the skeletal complaints of bone pains, spontaneous fracture and hypotonia, the general symptoms of lassitude, constipation and loss of weight, are rarely all present in any one case. They may well be due to other diseases than hyperparathyroidism; but the raised serum calcium and the lowered serum phosphorus levels are seldom found in any other disease. Even in children with skeletal decalcification due to disease such as anterior poliomyelitis, the raised serum and urinary calcium levels are accompanied by a normal or raised serum phophorus level. The definition of a raised serum calcium level is often the difficult question. Amongst the Mayo Clinic patients, 13% had a serum calcium level of less than 11 mg. per 100 ml., and 54% had levels of less than 12 mg. per 100 ml. When corrections have been made for the serum protein level, if the serum phosphorus level is depressed and the daily urinary output of calcium on a calcium-free diet is over 200 mg., a presumptive diagnosis of hyperparathyroidism may be made; but these estimations must be repeated several times before the physician can tell the surgeon to remove an adenoma, even if it means splitting the sternum to do so. It is in the patient with only a slightly raised serum calcium level that a clear picture must be obtained of calcium intake and excretion. Due allowance must be made for the change which impaired renal function will bring about, such as an increase in the serum phosphorus level and diminished calcium excretion in the urine.

The estimation of the serum alkaline phosphatase content is added information, but gives an indication only of osteoclast activity. The level may be raised in several bone diseases such as osteitis deformans, in hyperthyroidism and, of course, in obstructive jaundice. In the case of malignant parathyroid tumour, osteoclast activity must have been great; yet the serum alkaline phosphatase level was normal.

A positive result from a Sulkowitch test for urinary calcium in a patient on a diet of low calcium content is a simple indication for the initiation of more detailed studies. This test may give positive results in Paget's disease and in toxic goitre.

The typical features of the radiological appearance of the skeleton, found in about 25% of cases in most series, are widespread decalcification, subperiosteal and endosteal areas of bone resorption, and the "cystic" areas best seen in the long and short bones. In two of our cases, attention was directed to the disease first by the occurrence of fracture. In one of these there were no renal calculi. Sometimes cases are found in dental clinics. The absence of a clear lamina dura around the teeth points to skeletal decalcification. The cellular masses which Hunter and Turnbull (1931) called osteoclastomata may form an epulis. The teeth are not decalcified.

X-ray examination of the skull shows general decalcification with some cortical cysts. These are unlike the punched-out areas of multiple myelomata or malignant metastatic deposits. The clear, though pale, outline of the bone is unlike the fluffy appearance seen in Paget's disease.

One of our patients, who was referred by Sir William Morrow and whose case is reported elsewhere (Wyndham, 1958), had been treated previously for renal calculi and then for arthritis for a long period. The deformities due to skeletal weakening and muscle hypotonia have been mistaken for osteoarthritis or rheumatoid arthritis.

Other departments of clinical medicine may be concerned in the diminution of auditory acuity, the difficulty in accommodation and the calcium deposits in the conjunctiva or periphery of the cornea. Cataract is a well-known complication.

Can the tumour be located before operation? In none of our cases was this possible; but palpable tumours have

been reported, and X-ray examination by means of a barium bolus or arteriography is advised.

Treatment.

Only two things should be allowed to postpone operation. One is doubt as to the diagnosis, and the other is some complication which would make a reasonably safe operation impossible. It is sometimes necessary to operate on very ill patients. The Massachusetts General Hospital experts are emphatic that the preoperative administration of large doses of calcium not only fails to replenish the skeleton, but increases the risk of renal damage. Similarly, the use of phosphates to diminish the serum calcium level may only throw a greater strain on the already overloaded renal mechanism for phosphate clearance.

The whole operation need not be described, but important points require comment. Firstly, most surgeons defer mediastinal exploration, when indicated, to a second stage. The search for an adenoma or the identification of four cervical parathyroid glands may occupy two hours. In only one case was the mediastium explored by sternal splitting. This was done at the same operation as the neck exploration. We can seen nothing against this. Adequate exposure is obtained by immediate division of the infrahyoid muscles, and in some cases of the sternomastoid muscles. The cervical field is limited proximally by the level of the uppermost tip of the upper pole and distally by the upper part of the mediastinum. Laterally one goes as far as the lateral border of the carotid sheaths. The glands will be between the prevertebral fascia posteriorly and the investing layer of the deep cervical fascia anteriorly. Careful inspection, based on experience in the appearance of the gland, is of greater importance than brilliant dissection. Subcapsular hæmorrhage caused by the gentlest trauma from a pair of forceps will render a parathyroid gland unrecognizable. It is convenient to divide the upper pole on one side, search for the superior parathyroid gland on that side and then make a careful, but rather rapid, inspection of the lower part of the gland. The other side is examined in like manner. Some adenomas can be found in a few minutes. If such is not the case, then a complete careful dissection must follow. We have not gained much useful information from digital exploration of the mediastium from the neck, though many surgeons appear to do this. Exploration, under vision, of the upper mediastinum from the neck is, of course, advantageous. If one parathyroid gland cannot be found, it may be justifiable to remove the thyroid lobe on that side. We admit that we often await anxiously the pathological report on frozen sections of tissue removed at operation.

The mediastinal exploration is done through a curved incision through the sternum, which passes from the suprasternal notch to the third right intercostal space. The upper mediastinum is completely cleared, and the great vessels are examined on all their aspects. It is likely that inferior parathyroid glands may lie in the anterior mediastinum, while superior ones are sometimes found in the posterior mediastinum. The only gland we found in the anterior mediastinum was the right inferior one. It had no obvious arterial twig from the inferior thyroid artery. We failed in this case to find any adenoma, and we think that the gland involved is the left inferior one, which we failed to identify. In one case the left superior parathyroid gland lay behind the gullet at the thoracic inlet. Several anatomical hazards exist. The recurrent laryngeal nerve is obviously in danger. One was damaged in our series. The right pleural cavity was also opened in one case. The amount of tissue to be removed is considered in the discussion of tetany. Sometimes, in the best of hands, the tumour may not be found.

Arteriography has been used to demonstrate the gland, but we have not used it in the present series.

Post-Operative Care.

It is unnecessary to discuss those aspects of post-operative care which would apply to any operation in this part of the body. The vital question is the reestablishment of normal calcium metabolism. It is usual for the recovery period to be uneventful. Calcium disappears, or almost disappears, from the urine, the urinary phosphorus level falls and the serum calcium level falls to normal or slightly lower than normal. The serum phosphorus level is slow to recover normality and may even fall a little before doing so. Albright believes that the intracellular fluids may hold the phosphates.

In some cases the serum calcium level falls to 7 mg. per 100 ml., when tetany will usually ensue, though this was not so in Case V. It is very likely to occur in those patients with marked calcium depletion of the skeleton, as shown by X-ray examination and the raised alkaline serum phosphatase level. It is not especially related to the pre-operative serum calcium level or to the size of the tumour. The absorption of calcium by the depleted skeleton may be so rapid that it becomes impossible to maintain the serum calcium level above the limit below which tetany will occur. It is known that radioactive calcium can be detected in the bones 40 seconds after its intravenous injection.

Post-operative treatment, then, is centred around this problem. Measures to combat it may be preventive or curative. Prevention involves mainly an awareness of the possibilities in each case. Thus, when post-operative tetany is expected, partial resection of the adenoma has been advised by some workers. We have not done this, but have always removed all abnormal material regardless of the metabolic state of the patient. The size of the tumour seems to be unrelated to the severity of symptoms. Yet the patient who was suffering from the greatest possible calcium depletion had a large adenoma removed with no post-operative metabolic trouble, despite a minimum of therapeutic precautions.

Curative measures involve the administration of calcium and frequent examinations to indicate the changes in the serum calcium level. The probable futility of pre-operative calcium therapy in order to satisfy the requirements of a depleted skeleton has already been mentioned; but after operation everything should be ready to give calcium by mouth or intravenously should the need arise. When tetany is anticipated, calcium should be given before signs or symptoms appear. A diet rich in calcium and poor in phosphorus is given, and calcium in the form of calcium gluconate is added. A more certain method is to start a course of intravenous infusions of 5% glucose solution, with the addition of 100 ml. of 10% calcium gluconate solution in each 1000 ml. This can be given at any desired rate until the crisis has been passed. Meanwhile, repeated estimations of the serum calcium level and repeated tests for the pre-tetanic signs of Chvostek and Trousseau are made. Despite these precautions, in one case in the series it was very difficult to maintain a normal serum calcium level.

CASE V.—A woman, aged 62 years, broke her left femur when she stumbled without falling. She was admitted to Royal Prince Alfred Hospital in September, 1951, under the care of Mr. Hugh Barry. She had complained of rheumatic pains for five years and of loss of energy for two years. For six months before her admission to hospital she had been using a stick for walking because of pain in the left thigh. There was marked skeletal deformity, with impairment of breathing. A diagnosis of hyperparathyroidism was made and confirmed by X-ray examination, which showed a general decalcification of the skeleton. Investigation gave the following information: serum calcium level, 14 mg. per 100 ml.; serum phosphorus level, 2·4 mg. per 100 ml.; total protein content, 5·7 grammes per 100 ml.; serum alkaline phosphatase level, 43·2 King-Armstrong units. During the pre-operative investigation period, the highest serum calcium level was 19 mg. per 100 ml. At operation, an adenoma was removed from the position of the left inferior parathyroid gland. This consisted of both principal and chief cells. The serum calcium level had fallen to 10·2 mg. per 100 ml. by the next day, and five days later was 6·8 mg. per 100 ml. This fall occurred in spite of all measures to prevent it. Twelve days after operation the level had fallen to 5·3 mg. per 100 ml., until which time no tetany had developed and the cuff test had given negative results. Tetany did not occur until the fourteenth day. Treatment was made difficult by persistent post-

operative vomiting of unknown cause, and by what proved to be an overwhelming pneumonia due to aspiration of pharyngeal contents.

Albright (1948) places no faith in parathormone injections and very little in "AT10" or vitamin D for the restoration of serum calcium level. We can see nothing against their use. Vitamin D can be given over a long period, and this should be done, since it may take months to restore the skeletal calcium.

CASE VI.—A woman, aged 66 years, complained for five years of skeletal and joint pains with increasing deformity until the correct diagnosis was made at the arthritis clinic of the Royal Prince Alfred Hospital. On her admission to hospital she had marked upper thoracic kyphosis and rheumatoid swelling of the metacarpo-phalangeal joints. Her general condition was not good. There were râles at the base of the right lung, and ankle œdema. Her heart was enlarged. The Sulkowitch test gave positive results. Investigation revealed poor renal function a serum alkaline phosphatase content of 147 King-Armstrong units, a serum calcium level of 12·4 mg. per 100 ml., and a serum phosphorus level of 3·05 mg. per 100 ml.

After a prolonged biochemical investigation, operation was performed on February 11, 1954, and a large adenoma of the right inferior parathyroid gland was removed. This was composed of all the varieties of cell described earlier but mostly of the pale oxyphil type. Calcium was given intravenously and orally as a prophylactic measure after operation, and this succeeded in preventing postoperative hypocalcæmia. Unfortunately, the patient developed severe pulmonary infection, and also dermatitis of exfoliating type controlled by ACTH. One month after operation, tetany developed for the first time. This was controlled by the intravenous administration of calcium, but it was with difficulty that her serum calcium level was maintained at the normal figure. When she was discharged from hospital, 250,000 units of vitamin D and 20 mg. of calcium lactate daily were prescribed. Her serum calcium level was 9·8 mg. per 100 ml. and her serum phosphorus level 3·94 mg. per 100 ml. Four months after the operation she tripped and fell and fractured her os calcis. Her serum calcium and phosphorus levels were at that time estimated to be normal, but a serum alkaline phosphatase level of 45·7 King-Armstrong units indicated that the calcium requirements of her skeleton had not yet been met. This level did not return to normal for another month—that is, five months after the operation. However, nine months after the operation there was still evidence of decalcification of the skeleton, and in the kidneys faint calcified opaque areas were present, consistent with the clinical diagnosis of nephrocalcinosis.

Prognosis.

When the hyperplastic adenoma or hypertrophied glands have been removed, the patient must be guided back to health. This may require very few metabolic studies; but, on the other hand, these may be necessary for some weeks afterwards. If operation is unduly delayed, serious renal damage may result, and our first patient died some time after operation from suppurative pyelitis and renal failure. There was one death three weeks after operation from inhalation bronchopneumonia, but otherwise the post-operative recoveries in our series have been uneventful. This does not mean that the greatest care should not be exercised in the post-operative management of these patients.

We believe that the disease was well advanced in most of the patients in our series. The prognosis in the undiagnosed cases may be hard to estimate. It is likely that people may live for years with low-grade disturbances of calcium metabolism, without ill health. They merely consume sufficient calcium to save skeletal depletion, and exist as patients with recurrent calculi or slowly advancing impairment of renal function.

Summary.

A review has been given of the main features of hyperparathyroidism; the pathology, surgical experiences and problems in management have been discussed in the light of nine cases.

The opinion is expressed that there are undiagnosed cases in the community, and it is hoped that this paper will stimulate further interest in the subject.

Acknowledgements.

We are grateful to Dr. Lee Day for her investigation in the first of the eleven cases which came under our care, and especially to Professor C. R. B. Blackburn and the staff of the clinical research unit of the Royal Prince Alfred Hospital for investigating patients referred to them and for the opportunity of operating on patients sent to them by others for investigation.

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ENUMERATION AND SIZING OF BLOOD CELLS BY MEANS OF ELECTRICAL GATING.

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THE introduction of electrical gating in 1957 (Mattern *et alii*, 1957) into the design of apparatus intended for the counting of blood cells represents considerable progress in this field. It is notable that such apparatus obviates several of the sources of gross error inherent in counting-chamber methods which have been evaluated by Berkson.

Electrical gating offers the following advantages: (*a*) There is no chamber error associated with the vagaries occurring in flooding a counting chamber. (*b*) Field error as such is eliminated, and statistical errors of any sort are small on account of the large number of cells counted (50,000). (*c*) The method is rapid—these 50,000 cells are counted in 15 seconds. (*d*) The procedure is one of great convenience, and therefore eliminates observer fatigue and error.

The present purpose is to give an account of the operating characteristics of such an apparatus ("Coulter Counter").

Description of the Apparatus.

The apparatus (Figure I) consists of two parts, (*a*) the aperture assembly and (*b*) the electronic counting unit. The aperture assembly is shown in Figure II. In this diagram, E is the sample beaker, and A, which is the essential part of the whole apparatus, is an aperture leading into the tube B. Two electrodes C and D are situated inside the tube B and immersed in the liquid of the sample beaker respectively. The tube P leads to a suction pump. When the stopcock F is opened, fluid is drawn upwards through the orifice of the tube B, and also the fluid in the U-tube is drawn towards F. The liquid in the lower part of the U-tube is mercury (hatched). After the left-hand limb of the column of mercury has been drawn below K, the stopcock F is closed, whereupon the unbalanced mercury column, in returning to equilibrium, continues to draw liquid from the sample beaker through the orifice A into the tube B. As the mercury reaches the electrode L, the electrical connexion between K and L starts the counter working, and when the mercury reaches the electrode M this contact stops the counter. In this way the counter enumerates

ILLUSTRATIONS TO THE ARTICLE BY M. J. ETHERIDGE AND J. D. TANGE.

FIGURE I.

X-ray photograph of the chest showing dense pericardial calcification (lateral view).

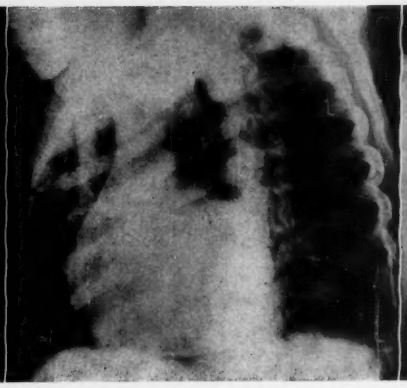


FIGURE II (*a*).

Case V: X-ray photograph of the chest, before operation in 1952, showing cardiac enlargement and pericardial calcification (left anterior oblique view).

FIGURE II (*b*).

Case V: X-ray photograph of the chest in 1955.

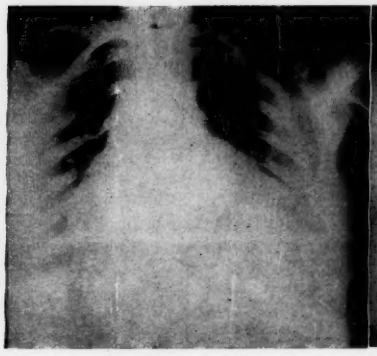


FIGURE VII (*a*).

X-ray photograph of the chest of a patient with tuberculous pericarditis, showing pleural and pericardial effusions.

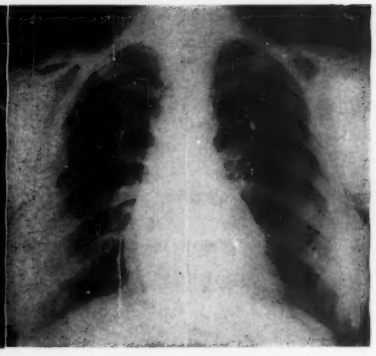
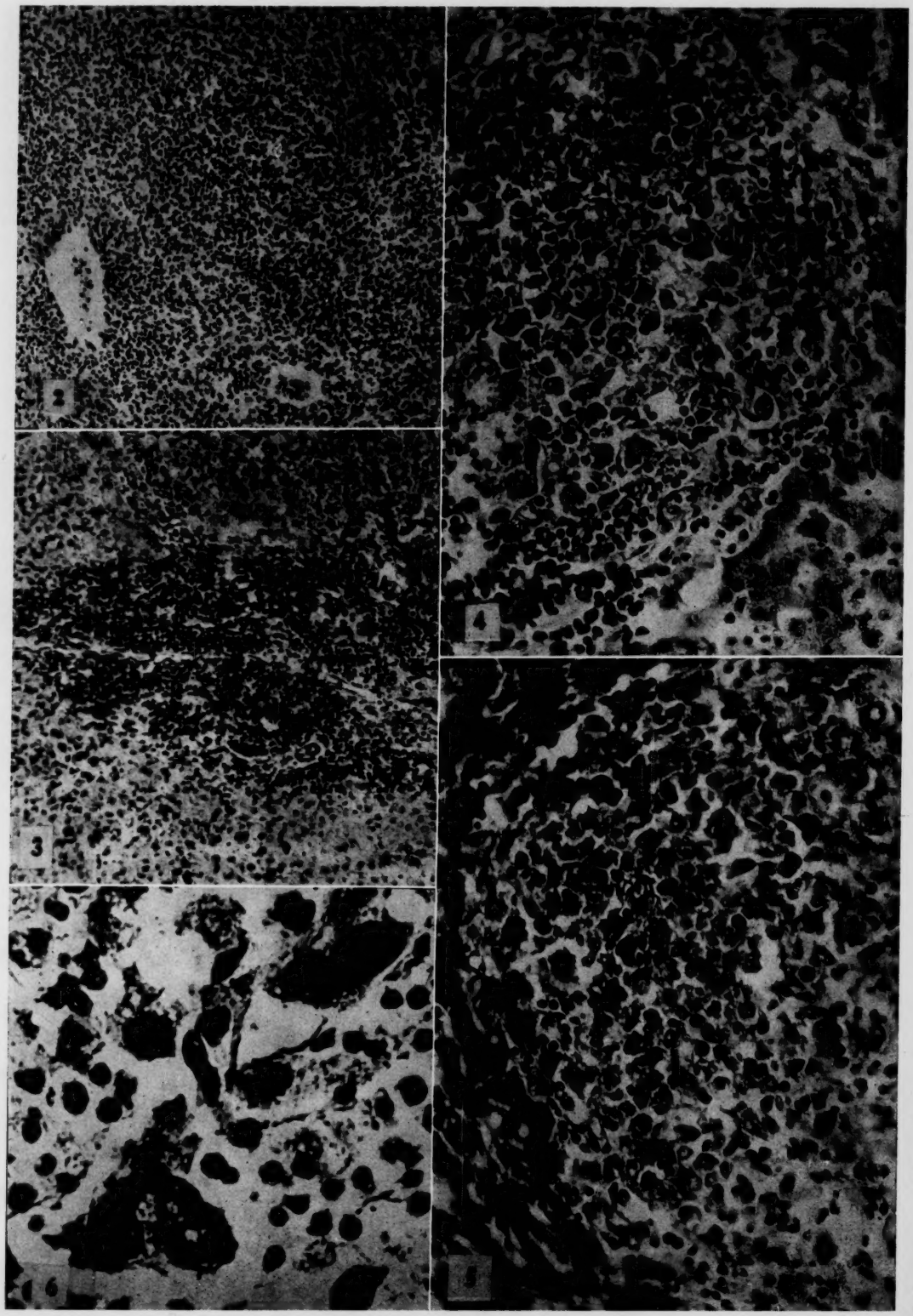


FIGURE VII (*b*).

X-ray photograph of the chest of the same patient seven years after pericardectomy.

ILLUSTRATIONS TO THE ARTICLE BY R. N. IBBOTSON AND C. W. KINGSTON.



cells in a fixed volume of liquid (0·5 ml.) corresponding to that volume between the electrodes M and L. The device provides an automatic and reliable method of measuring the volume of liquid passing through the orifice A. The principle of counting depends upon using a very high dilution of blood, actually 1 in 50,000 for red blood cells, so that in general one cell passes through the orifice A at a time. The cells are suspended in an electrically conducting fluid (physiological normal saline),

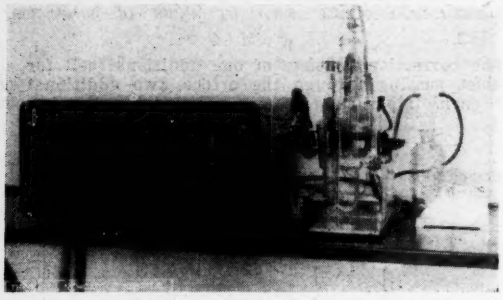


FIGURE I.

and during counting there is a potential difference between the electrodes C and D. Each cell passing through the orifice generates an impulse in the electric current flowing between C and D, owing to the fact that the cell is of different electrical conductivity from the suspending fluid. These impulses are fed by means of the leads H and I

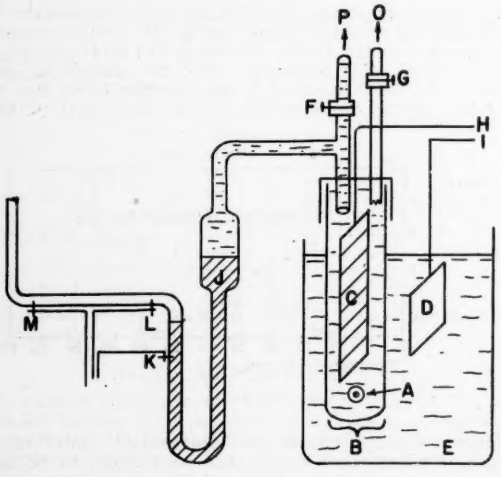


FIGURE II.

into the counting apparatus. The counting unit is shown diagrammatically in Figure III. The electrical impulses reaching the counter operate upon both an oscilloscope and a digital counter. As each cell passes through the orifice, a spike is produced on the oscilloscope S, so that during counting a pattern is readily available for inspection. The impulses reaching the digital counter are registered on the digital register R. The register makes provision for six digits, the units, tens and hundreds being recorded by small electric lamps and the other digits mechanically. The image on the oscilloscope screen can be centred by means of adjusting knobs inside the box, as can also the brightness. Once these adjustments have been made, the controls do not require day-to-day adjustment. The size of the impulse generated by the cell passing through the orifice depends upon the aperture current as well as upon the cell. Adjustment of the aperture current by means of knob U allows the size of the spikes to be adjusted to suitable dimensions. Under working conditions, day-to-day adjustment is not needed.

According to the manufacturer's mathematics, with fixed aperture current the impulse generated is directly proportional to the volume of the cell. Further, the height of the spike is proportional to the impulse. The threshold setting T determines the magnitude which an impulse must reach in order to be counted by the digital

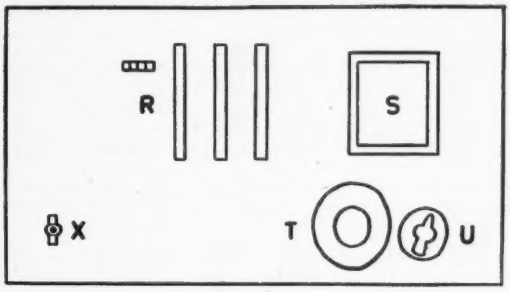


FIGURE III.

counter. Thus, in counting red blood cells, the threshold setting is set at 10. The effect of this is that the impulses generated by particles smaller than red blood cells are neglected by the counter, although they are visible on the oscilloscope screen as small spikes. On the other hand, the impulses generated by the red blood cells,

TABLE I.

Saline Background Counts.

Aperture current setting: 6.

Threshold Setting.	Machine Counts.
5	743
10	351
15	275
20	216
25	149
30	104
35	79
40	72
45	47
50	48

which are considerably larger and exceed this threshold, are counted. The level of the threshold is indicated on the oscilloscope screen by a reduced intensity of the image below the threshold level. This visible demarcation provides a ready check that the threshold is set at a satisfactory level, and in the case of a red cell count it can be seen that there is a very wide margin between impulses that it is desired to count and those that it is not desired to count. When a count is about to be commenced, the switch X is moved. This clears the digits of the previous count from the digital register, and reverses the current between the two electrodes immersed in the sample beaker and tube. The purpose of this reversal of current is to minimize polarization effects on the electrodes. The counting is automatically started and stopped at the appropriate moments in the manner already described.

Interesting points arising from the foregoing description are: (*a*) The apparatus is a true particle counter, taking note of each individual particle, and does not depend upon effects of masses of particles, such as opacity or diffraction. (*b*) There is no optical system, and photocells are not required to convert light impulses to electrical impulses for electronic counting. (*c*) A counting chamber is not used, and consequently no mechanical device is

required to move such counting chamber across a light path. (*d*) The operation of the apparatus is extremely simple. The diluted sample is put into the sample beaker, the mercury column is brought into the initial position for counting, the switch on the counting apparatus is turned and the digital register is read at the end of the count (approximately 15 seconds).

Coincidence Error.

While a high dilution is used, so that in general one cell goes through the orifice at a time, chance decrees that on occasions there will be two, three or even more

TABLE II.

Normal Blood, Red Blood Cells 5,490,000 per Cubic Millimetre, Hæmatocrit.

Threshold.	Machine Count.	"Corrected" Count.	Mean Threshold $\bar{t}_{\Delta_n}$.	Increment (10^6 per Cubic Millimetre). Δ_n.	Product. $\Delta_n \bar{t}_{\Delta_n}$.
5	48,234	54,200	—	—	—
10	48,886	54,900	7·5	0·0	0·0
15	47,279	53,100	12·5	0·18	2·25
20	37,800	41,500	17·5	1·16	20·30
25	23,474	24,600	22·5	1·69	38·02
30	13,847	14,300	27·5	1·03	28·32
35	7332	7300	32·5	0·70	22·75
40	4225	4200	37·5	0·31	11·62
45	2414	2400	42·5	0·18	7·65
50	1463	1400	47·5	0·10	4·75
55	1041	1000	52·5	0·04	2·10
60	680	600	57·5	0·04	2·30
				$\Sigma(\Delta_n)\bar{t}_{\Delta_n}$	=140·06

[1] $V_p = f\Sigma(\Delta_n)\bar{t}_{\Delta_n}$; $0{\cdot}46 \times 10^9 = 140{\cdot}06 \times 10^6 f$; $f = 3{\cdot}3$ c.μ per unit. Mode at $22 \times 3{\cdot}3 = 73$ c.μ.

Mean corpuscular volume $= \frac{0{\cdot}46 \times 10^9}{5{\cdot}49 \times 10^6} = 84$ c.μ.

cells at once within the orifice. In such instances the group of cells produces one impulse, which is counted as one cell by the counter and throws an extra large spike on the oscilloscope. Such events lead to what is called the coincidence error. The probability of there being

TABLE III.

Normal Blood, Red Blood Cells 5,490,000 per Cubic Millimetre, Hæmatocrit 46%.[1]

Threshold.	Machine Count.	Groups Counted.	Singles Counted.	Mean Threshold. $\bar{t}_{\Delta_n}$.	Increment. (10^6 per Cubic Millimetre). Δ_n.	Product. $\Delta_n \bar{t}_{\Delta_n}$.
5	48,234	5693	42,541	—	—	—
10	48,886	5693	43,193	7·5	0·0	0·0
15	47,279	5693	41,586	12·5	0·16	2·00
20	37,800	5693	32,107	17·5	0·95	16·59
25	23,474	5693	17,781	22·5	1·43	32·23
30	13.847	5693	8154	27·5	0·96	26·47
35	7332	5693	1639	32·5	0·65	21·17
40	4225	5693	0	37·5	0·64	6·15
45	2414	—	—	42·5	0·0	0·0
50	1463	—	—	47·5	—	—
55	1041	—	—	52·5	—	—
60	680	—	—	57·5	—	—
					$\Sigma(\Delta_n)\bar{t}_{\Delta_n}$	=104·61

[1] Hæmatocrit adjusted for singles counted $46 \times \frac{4{\cdot}31}{5{\cdot}49} = 36\%$; $V_p = f\Sigma(\Delta_n)\bar{t}_{\Delta_n}$ $0{\cdot}36 \times 10^9 = 104{\cdot}62 \times 10^6 f$; $f = 3{\cdot}5$ c.μ. per unit. Mode at $22 \times 3{\cdot}5 = 77$ c.μ. Mean corpuscular volume $= \frac{0{\cdot}36 \times 10^9}{4{\cdot}3{\cdot}1 \times 10^6} = 84$ c.μ.

0, 1, 2 or more cells in the orifice can be represented by a series of values P_0, P_1, P_2, P_3, . . . P_N, the sum of which is unity, as it is absolutely certain that one or other of these events will occur (equation 1).

$$1 = P_0 + P_1 + P_2 + P_3 + \ldots \quad (1)$$

The numerical values of the terms of this series are given by the classical Poisson distribution, where e is the natural logarithmic base and m is the average number of cells to be found in the volume of the orifice (equation 2).

$$1 = e^{-m} + me^{-m} + \frac{m^2}{\lfloor 2} e^{-m} + \frac{m^3}{\lfloor 3} e^{-m} + \ldots \quad (2)$$

The true count is thus the machine count plus a correction. In equation 3, M = machine count, C = correction, V = true count.

$$V = M + C \quad (3)$$

The correction consists of one additional cell for each doublet passing through the orifice, two additional cells for each triplet and three additional cells for each

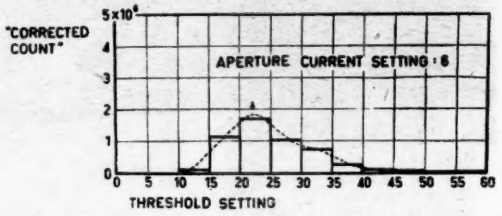


FIGURE IV.

quadruplet, and so on. This may be expressed as in equation 4, where D is the number of doublets, T triplets, Q quadruplets.

$$C = D + 2T + 3Q + \ldots \quad (4)$$

The true count has been tabulated by the maker for each observed machine count, and is very simply obtained by reference to the tables. Owing to the large number of cells counted, the correction may be considered quite reliable. In this connexion it may be mentioned that the effective volume of the orifice is not the actual physical

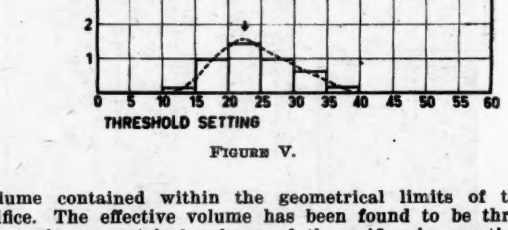


FIGURE V.

volume contained within the geometrical limits of the orifice. The effective volume has been found to be three times the geometrical volume of the orifice in question. This, of course, is due to the fact that when cells come near the orifice they are able to disturb the electrical conductivity, as well as when they are actually within its geometrical limits. For purposes of future calculation, it may be noted that the effective volume of the orifice in question, which has a geometrical diameter of 100μ and a geometrical length of 75μ, is given by E in equation 5.

$$E = (3 \times \pi \times 50^2 \times 75)\ \text{c}\mu = 1{\cdot}96 \times 10^6\ \text{c}\mu = 1{\cdot}96 \times 10^{-3}\ \text{c.mm.} \quad (5)$$

Red Cell Counts.

In order to count red cells, the blood is diluted 1:50,000 with 0·9% saline (0·002 ml. of blood in 100 ml. of saline). As 0·5 ml. of fluid passes through the orifice in each count, 50,000 cells will pass through this orifice, in the case of a blood containing 5×10^6 red cells per cubic

millimetre. The threshold of the instrument is set at 10, so that the particles smaller than the red blood cells may be ignored. White cells, of course, are counted with the red cells, but they are numerically insignificant except in cases of leukæmia with an extremely high count. The recorded impulses are read off the digital registers, and reference to the coincidence error tables gives the true count in millions per cubic millimetre after the decimal point has been suitably placed. Observation of the oscilloscope confirms the fact that the threshold is far above the small spikes close to the base line which are generated by small particles, and the oscilloscope

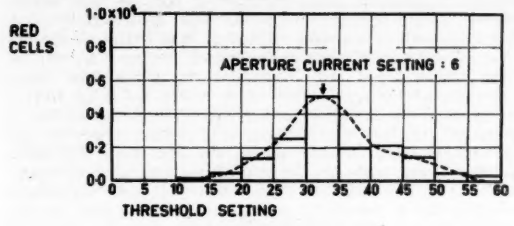


FIGURE VI.

pattern also informs the observer whether the cells are normocytic, microcytic or macrocytic.

Background Count.

A very low count is obtained by running through the saline solution prepared in the laboratory for use with the electronic counter. The saline is as a routine measure filtered through Whatman paper No. 1. Examples of the

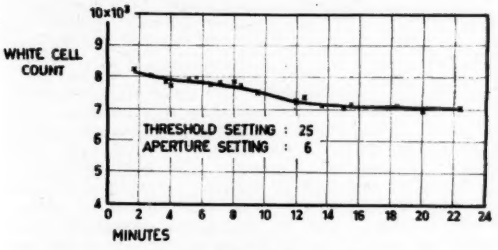


FIGURE VII.

counts obtained are given in Table I. These figures are insignificant as a source of error.

Sizing Red Blood Cells.

The makers claim that as the impulse is proportional to the cell volume, it is possible to calibrate the threshold setting of the instrument with respect to cell size by means of the equation 6.

$$6. \qquad V_p = f\Sigma\ (\Delta_n)\ \bar{t}_{\Delta_n}$$

In this equation V_p is the total particle volume (in the case of the red blood cells measured by the hæmatocrit), f is the desired conversion factor, Δ_n is the increment of the red cell count over each threshold change, and $\bar{t}_{\Delta_n}$ is the mean threshold value corresponding to the increment being considered. For this calculation, the increments of n are to be obtained by making a series of machine counts each at different threshold settings, referring to the correction tables for the true count and taking differences of these results. Figures for normal blood derived in this way are set out in Table II. Calculations from this table give a value for f of 3·3. Figure IV gives the histogram derived from Table II, with a sketched-in dentistry distribution curve. The mode, at a threshold setting of 22, corresponds to a mean corpuscular volume of 73 $c\mu$ on the basis of f being equal to 3·3. The curve shows considerable spread and is quite asymmetrical, rather more asymmetrical than one might have expected from previously seen Price-Jones curves (Whitby and Britton, 1946; Dacie, 1951). Because of the asymmetry, the mode of 73 $c\mu$ is at a distance from the average corpuscular volume of 84 $c\mu$ as calculated in the usual way.

Review of Calculation.

In considering possible explanations of this marked departure from symmetry, the method of calculating the increments was considered and fell under suspicion. In estimating the corrected counts from the machine count, the coincidence error tables were applied directly. However, it is clear, that with progressive increase in the threshold settings of the instrument, although the machine counts became progressively less, in actual fact the same number of cells went through the orifice and no doubt the same number of doublets and triplets, etc. Thus the supposed correction deviated further from the truth as the machine count became less. For this reason, the sum of the number of doublets and triplets, etc., was

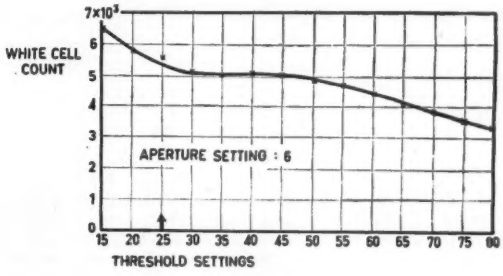


FIGURE VIII.

calculated by means of the data of equations 2, 3, 4 and 5, and this same figure (5693) was subtracted from the instrumental count at each threshold reading (see Table III). In this way, an estimate was obtained of the number of single cells counted at each threshold setting on passing through the orifice. The number of groups of cells was calculated by the following steps. The average number of cells m in the orifice was obtained as in equation 7 from the true count per cubic millimetre divided by the dilution multiplied by the effective volume of the orifice.

$$7. \qquad m = \frac{5{\cdot}5 \times 10^6}{5 \times 10^4} \times 1{\cdot}96 \times 10^{-3} = 0{\cdot}21$$

By the use of this value of m, the relative numbers of doublets, triplets and quadruplets, etc., can be calculated from equation 2 ($T = D \times 0{\cdot}073$, $Q = D \times 0{\cdot}004$), the value of the terms of the series rapidly diminishing. As can be seen from equation 4, the correction is equal to the number of doublets plus twice the number of triplets plus three times the number of quadruplets, etc., so that the number of the doublets can be calculated as in equation 8. The correction C is equal to $(54{,}900 - 48{,}886)$.

$$8. \qquad 6114 = D + 0{\cdot}146\,D + 0{\cdot}0120\,D$$

whence $D = 5286$
$T = 386$
$Q = 21$

Total groups 5693

Thus, doublets plus triplets plus quadruplets are equal to 5693. The number of single cells counted at each threshold can then be obtained by subtracting 5693 from each instrumental reading as in Table III. From this table the increments are deduced as before, and Figure V shows the histogram derived from these calculations. In calculating f in this case, the value of the V_p has to be

adjusted for the single cells counted as in the calculation at the foot of Table III. The value of f is now found to be 3·5. The mode, as before, is at the threshold setting of 22. By the use of the new value $f = 3·5$, this setting is found to correspond to a mean corpuscular volume of 77 cμ. This is somewhat closer to the average corpuscular volume of 84 cμ as calculated in the usual way. The curve is not so skew and the spread is very considerably reduced by cutting off the tail on the right.

Asymmetry of Curve.

If the curve is made symmetrical with respect to the left-hand side, it can be seen that this skewness is accounted for by 6526 cells or the equivalent of $0·65 \times 10^6$ cells per cubic millimetre in the original sample of blood. This is far too great a number to be accounted for by leucocytes or platelets in the agglutinated state. The coincidence correction of 6114 cells corresponding to $0·6 \times 10^6$ red blood cells in the original sample is of the same order. If one can assume simple additive properties with respect to combined cell size in a randomly assorted set of doublets, such an assortment will have the maximum of its density distribution curve at a threshold setting of 45, and about 60% of the doublets or the equivalent of $0·36 \times 10^6$ impulses per cubic millimetre will be found above the threshold setting of 40. Therefore the doublets do not seem to account for the asymmetry. It would appear that the red blood cell size is not symmetrically distributed about a mode. It was thought that this asymmetry might be due to young blood cells. To test this hypothesis, a series of readings was made in a case of post-hæmorrhagic anæmia. (The patient was a woman, aged 30 years, who had had a miscarriage with bleeding 10 days before the count. The red cell count was $1·69 \times 10^6$ per cubic millimetre, the hæmoglobin value 6 grammes per 100 ml., and the hæmatocrit 18%. At the time of examination the blood film exhibited polychromasia.) The graph, constructed by the method of Table III, is shown in Figure VI (the ordinate scale is increased fivefold). In this case, the mean corpuscular volume is 106 cμ and the mode is 100 cμ (in the calculation using these data $f = 3·1$). The spread of the curve is greater than that of the normal, and there is general displacement to the right. No second peak is discernible to the right of the main peak to suggest a crop of young red cells. It would appear that the already circulating cells have increased their volume by a factor of about 1·3 by some unknown means.

TABLE IV.

White Cell Counts.

Aperture current setting: 6.

Table IVA.

Sample Number.	Threshold.			
	15	25	35	45
1	10,393	9623	9213	8590
2	9912	9019	8682	8914
3	7658	6813	6550	5928
4	5996	5153	4791	4387
5	5853	4753	4608	4503
6	4767	4440	4447	4425
7	5731	5233	5276	5128

Table IVB.

Change of Threshold.	Mean Increment in Count.
15 to 25	754
25 to 35	65
35 to 45	385

Spread of Curve.

In contrasting the narrow Price-Jones curve with the broader curves obtained by the present methods, it should be noted that in the Price-Jones curve one measures cell diameter, whereas in the curves discussed in this article one is measuring volume. As volume is proportional to the cube of the diameter, the reason for the relatively wider volume distribution curve is obvious.

White Cell Counts.

In the case of the white blood cells, a dilution of 1:500 is used (0·2 ml. of blood in 100 ml. of saline), with the addition of a further 1 ml. of 1% saponin solution. The saponin leads to the destruction of the red blood cells in a few minutes, while the destruction of the white blood cells takes much longer. In the case of the white blood cells, considerably fewer are counted in the same volume (10,000 cells in 0·5 ml.), so that the use of the coincidence error correction tables is not necessary. In the white blood cell counts there is much more débris than in the case of the red blood cell counts because of the lysis of the red cells, and this is seen as thick "grass" along the base line on the oscilloscope. Consequently a threshold setting at 25 is made. In other respects the count is carried out as for the red cells. Figure VII shows the decline in white cell count with lapse of time. The sketched-in curve suggests a logarithmic decay, and on logarithmic paper the relationship appears to be linear. It can be seen that within 10 minutes there is a loss of not more than 10%, and even within 20 minutes the loss is not greater than 20%. Figure VIII shows the curve obtained by making as rapid a succession as possible of readings on the same blood at different threshold settings. The recommended threshold setting for white cell counts is 25, whilst inspection of the curve indicates that a flatter portion is to be found in the range of 30 to 45. This was checked by making similar observations over a shorter range on other specimens. The results are set out in Table IV. Possibly 30 would be a better threshold setting than 25 for the enumeration of white cells.

TABLE V.

Aperture current setting: 6; threshold setting: 10.

Dilution Number.	Count in Red Blood Cells per Cubic Millimetre. (Mean.)	Cells Actually Counted. (Mean.)	Variance.
1	$4·45 \times 10^6$	44,500	0·98%
2	$2·12 \times 10^6$	21,200	1·4%
3	$1·15 \times 10^6$	11,500	0·91%
4	$0·45 \times 10^6$	4500	1·8%

Coefficient of Variation.

The coefficient of variation was estimated from sets of six readings on each of four different red cell dilutions. The values obtained are set out in Table V.

Daily Routine.

The apparatus is flushed to remove accumulated cells and cell débris by opening stopcocks G and F and dipping a rubber tube connected to 0 (Figure II) into saline and allowing the pump to operate, thus drawing saline with suspended débris into a trap bottle inserted between the pump and the aperture assembly. Saline is as a routine checked for background count.

Orifice.

The diameter of the orifice is 100μ and its length 75μ. This is considerably larger than the red blood cells with a diameter of 7μ. The orifice dimensions seem to provide an adequate safeguard against blocking of the orifice by particulate matter. During operation, blocking occasionally becomes evident by slowing of the rate of counting, and in such a case withdrawal of the sample

beaker and sucking air through the orifice by means of the pump together with wiping of the finger over the orifice almost invariably frees the orifice. There is a small microsope attached to the aperture assembly which enables one to inspect the orifice. Occasionally, especially after the apparatus has been standing over the weekend, the orifice becomes blocked and is not unblocked by the foregoing procedure. However, soaking for several hours in 10% urea solution has allowed the orifice to be freed by the insertion of a camel hair from a brush.

Summary.

Apparatus for the electrical gating of blood cells allows both red cells and white cells to be counted electronically with great speed and accuracy. The process seems to be very reliable, and there is a satisfactory working check in the continuous inspection of the oscillograph screen. Further, red cell size can be estimated visually from the oscillograph screen possibly as accurately as from a blood film, and if a distribution curve of the red cell volume is desired it can be obtained by eight to ten readings. The ease of operation entirely eliminates operator fatigue, and day-to-day maintenance is negligible.

Acknowledgement.

The illustrations have been prepared by Miss J. McDonald, of the Illustration Section, Royal Newcastle Hospital.

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Addendum.

In the foregoing paper it will be noted that the values of the calibration factor *f* obtained with normal blood on different occasions varied from 3·1 to 3·5.

TABLE A.

Concentration Saline.	Value of *f*.
0·85%	3·6
0·90%	4·0
0·95%	4·1

To investigate this variation, experiments were undertaken to determine the effect of variations in the concentration of the saline and variations in the temperature. The values of *f* found with different concentrations of saline on the same occasion and at an ambient temperature of 26° C. were as shown in Table A.

TABLE B.

Temperature.	Value of *f*.
26° C.	4·0
37° C.	4·9

The differences in value of *f* may be explained in part by the actual change in size of red cells due to osmotic effects, and possibly in part by differences in "apparent electrical size" due to altered conductivity of the saline and also of the red cells. Except in 0·9% saline, the red cells are not measured by the hæmatocrit at the same size at which they are measured by the counter.

The effect of temperatures is even more striking, as is shown in Table B. In this experiment, the same concentration of saline (0·90%) was used; but the apparatus was warmed by drawing saline at 37° C. through the apparatus and by using for the dilution of blood saline which had previously been warmed at 37° C.

If it is desired to determine absolute values for size distribution curves of the red blood cells, it is clear that the value of *f* must be calculated on each occasion with the particular batch of saline in use equilibrated to the ambient temperature. In practice, normal blood may be run through at the same time.

Reports of Cases.

TRANSITION OF LYMPHATIC LEUKÆMIA TO RETICULUM CELL SARCOMA.

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ALTHOUGH the transition of some lymphatic tumours is fairly common, the combination of chronic lymphatic leukæmia and reticulum cell sarcoma has been recorded on very few occasions.

We should like to report here a disease which commenced as typical clinical and hæmatological lymphatic leukæmia, and in which the histological appearance of the marrow and spleen early in the disease confirmed this diagnosis and showed no evidence of reticulum cell hyperplasia. After an apparent clinical remission, the course of the disease altered somewhat, and autopsy revealed a histological picture of both leukæmic infiltration and reticulum cell sarcoma of the type often described as Hodgkin's sarcoma.

Clinical Record.

The patient, a butcher, aged 57 years, was first admitted to hospital in May, 1953. He gave a history of increasing lassitude over the previous nine months, during which period he had also suffered from numerous infected sores of the hands and feet. During the six weeks prior to admission he had lost 14 lb. in weight and had noticed increasing shortness of breath so that he had been unable to work. His past history included an episode of erythema nodosum in 1942, but an extensive and protracted search failed to reveal any evidence of tuberculosis. Between 1942 and 1953 he had had repeated attacks of bronchopneumonia and pleurisy, averaging one attack per year.

On examination the patient appeared healthy; he was in no obvious distress, and had mild finger clubbing. There were enlarged lymph nodes in the neck and in both axillæ and groins. Numerous rhonchi and râles were present at both lung bases. The liver was enlarged to three fingers' breadth below the costal margin, and the spleen was enlarged to the level of the umbilicus. The blood pressure was 135/80 mm. of mercury. Examination of the peripheral blood showed the hæmoglobin value to be 13·0 grammes per 100 ml.; red blood cells numbered 4,350,000 per cubic millimetre; the packed cell volume was 38%; the mean corpuscular volume was 87 cubic microns; the mean corpuscular hæmoglobin concentration, 34·5%; there were 40,000 white blood corpuscles per cubic millimetre, of which 2% were metamyelocytes, 21% polymorphs, 1% lymphoblasts, 75% lymphocytes and 1% monocytes. Sternal marrow aspiration yielded extremely cellular smears and sections, in which 80% of the nucleated cells belonged to the lymphatic series. There was no increase in the percentage of reticulum cells.

A diagnosis of lymphatic leukæmia was made, and a course of 6·6 mg. of nitrogen mustard was administered

intravenously in isotonic saline during June, 1953. A similar course was given ten weeks later, in September, 1953. At this time the patient's condition had deteriorated, there was an increase in the number and size of the cervical lymph nodes, and there was further enlargement of the spleen. A course of treatment with *Liquor Arsenicalis* was started. The patient was readmitted to hospital on two occasions in October, 1953, the second admission being complicated by an attack of herpes zoster of the seventh and eighth left thoracic segments. *Liquor Arsenicalis* treatment was discontinued in October, after this attack. Pain above the level of the herpes continued, and in December, 1953, six doses of 200*r* of deep X-ray therapy were given to the lower thoracic segment of the spine, with some subjective improvement. There was no radiological evidence of mediastinal involvement at any stage of the illness.

Apart from an infected finger, the patient remained well until August, 1954, when he developed bilateral pleurisy and bronchopneumonia; recurrent attacks of the same type followed in October and November, 1954. At this time the hæmatological condition deteriorated: the lymphocyte count rose to 193,000 per cubic millimetre, with 10,200 polymorphs per cubic millimetre, and the hæmoglobin content of the blood fell to 8·7 grammes per 100 ml. Deep X-ray therapy (450*r*) was administered to the spleen in January and February, 1955. In March, 1955, repeated blood transfusions became necessary, and a hæmolytic process related to splenic activity was suspected. Red cell survival studies by means of the Ashby technique showed a mean survival time of 28 days (normal, 120 days). The direct Coombs test gave a negative result. Splenectomy was performed on April 25, 1955. This was followed by general improvement and there was no further evidence of hæmolysis, so that transfusion was not required again during the remainder of the patient's life (Figure I). Histologically, the spleen showed a picture consistent with lymphatic leukæmia, with a uniform replacement of all cells by small round cells resembling immature lymphocytes. There was no evidence of reticulum cell hyperplasia (Figure II).[1]

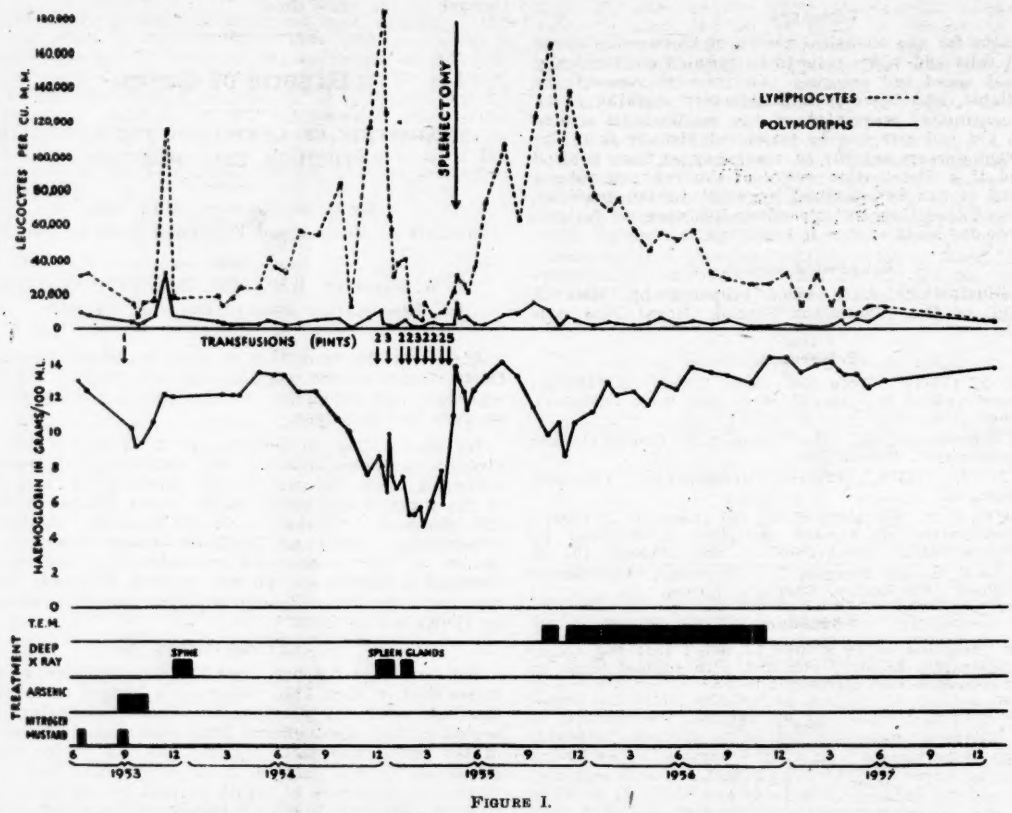

FIGURE I.

Showing the variations in the lymphocyte count, polymorph count and hæmoglobin value during the course of the illness, with their relation to treatment.

In October, 1955, a course of triethylene melamine (2·5 mg. per day) was commenced, and apart from one interruption during an episode of bronchopneumonia in November, 1955, this dosage was continued for 13 months until November, 1956. It was discontinued when a small gastric ulcer was found on barium meal X-ray examination. During this period there appeared to be a good hæmatological remission, the lymphocyte count fell from 147,000 to 25,000 per cubic millimetre, and the lowest polymorph count was 1300 per cubic millimetre. In March, 1957, the patient was admitted to hospital with symptoms of meningitis. Lumbar puncture was performed; the cerebro-spinal fluid contained 15,000 cells per cubic millimetre, of which 90% were lymphocytes. The fluid was sterile. A good clinical response followed penicillin and streptomycin therapy.

In May, 1957, serum electrophoresis showed that the gamma globulin content was reduced to 0·4 gramme per 100 ml. (normal, 0·7 to 1·0 gramme per 100 ml.). The albumin content was within normal limits, and the alpha-1 and alpha-2 globulin levels were slightly raised.

The final hospital admission took place in January, 1958, with a further attack resembling bronchopneumonia. This

[1] For Figures II to VI see art-paper supplement.

attack did not appear to respond to treatment, and the patient's general condition slowly deteriorated until he became comatose and finally died on February 18, 1958.

Autopsy was performed about 20 hours after death. The body was in a poor state of nutrition, and the usual signs of death were present. The cervical, axillary and femoral lymph nodes were not palpable. There was an oblique subcostal operation scar in the left hypochondrium. The neck, the upper part of the respiratory tract, the mouth, the œsophagus and the alimentary tract were normal. The pleural cavities were clear. The lungs were emphysematous, with marked congestion of the lower lobes, and pus could be expressed from the smaller bronchi. The heart was small, flabby, and brownish in colour; the valves, chambers and myocardium were normal. There was little atheroma of the coronary arteries or the aorta. The liver was enlarged and pale, and showed on its capsular surface and its cut surface a somewhat uniform pattern of small translucent infiltrations corresponding roughly to the lobular pattern. The spleen was absent, but there was a small splenunculus in the splenic bed, 2·5 cm. in diameter. There was no significant abnormality of the urogenital or nervous system. On dissection of the lymphatic system, the cervical lymph nodes were a little enlarged and the mediastinal and internal mammary nodes were moderately enlarged, varying in size up to 2 cm. The abdominal lymph nodes were considerably enlarged; most of the nodes were separate, but those of the iliac and aortic chains tended to be matted together, varying in diameter up to 7·0 cm. The larger lymph nodes, particularly around the inferior vena cava, were markedly hæmorrhagic. On section, the others were all uniform yellowish-white and fish-flesh in appearance.

Histological Examination.

The Liver.

The liver cells showed an increase of bile pigment and in some places obstruction of canaliculi by bile thrombi. There were infiltrations following the lobular pattern throughout the organ, situated mostly around the portal tracts. These infiltrations took three forms: (i) pure lymphoid, consisting of collections of small round cells only, resembling immature lymphocytes (Figure III); (ii) mixed lymphoid and reticulum cells, the reticulum cells occupying the centre of the infiltration, the lymphocytes being confined to the edge with very little admixture of the two types and no evidence of transition (Figure IV); (iii) pure reticulum cell infiltrations (Figure V). In the two last-mentioned forms the reticulum cells were large malignant cells with large hyperchromatic vesicular nuclei and prominent nucleoli. Many of the cells were multinucleated, with the nuclei tending to be central; there were two to five nuclei per cell. Some of these were binucleated with mirror-image type of reniform nuclei resembling Sternberg-Reed cells (Figure VI). Mitoses were fairly numerous. Appropriate staining showed no marked increase of reticulum.

Sternal Bone Marrow.

There was a little hæmatopoietic tissue present in the sternal bone marrow, but most of the tissue was replaced by reticulum cells similar to those described above, the cells here being larger, the nuclei larger, and more of the cells multinucleated. There were scattered lymphocytes throughout.

Lymph Nodes.

The normal architecture of the lymph nodes was completly lost. The cellular elements were almost entirely reticulum cells similar to those described above. There were bands of widely spaced lymphocytes, mostly situated along fibrous trabeculæ. There were a few areas of central necrosis.

Myocardium.

There were some lymphoid infiltrates, particularly around blood vessels, in the myocardium and epicardium.

Other Organs.

The splenunculus was almost completely fibrotic. The lungs, suprarenals, thyroid and kidneys showed no significant change.

Discussion.

Transitions of lymphomatous tumours have often been reported in the literature, but certain of these are much more common than others. For example, the development of a leukæmic blood picture in the later stages of lymphosarcoma is not uncommon and has long been recognized. Similarly, the propensity of follicular lymphomas to develop into lymphosarcoma, reticulum cell sarcoma and Hodgkin's sarcoma is also well known. Rappaport *et alii* (1956) reported 24 examples of a change to lymphoblastic and reticulum cell types in a series of 253 cases of follicular lymphoma from the American Armed Forces Institute of Pathology. They pointed out that the nature of the transition could often be predicted from the nature of the cellular composition of the original tumour. Custer and Bernhard (1948), in reviewing 1300 lymphatic tumours from the same institute, found a striking fluidity of histological pattern in tumours sampled several times during their progress. They interpreted their findings as indicating a single neoplastic entity covering all the lymphoid tumours and having a number of variants. From their data they drew up a schematic diagram indicating the interconversion of these tumours. Again they noted that some changes were much commoner than others; but the change described in our case was not indicated in their schema, and presumably did not occur in their series.

The task of discussing transitions in these tumours is made extremely difficult by the equal fluidity in classification and nomenclature used by writers in this field. Only those which appear relevant to the discussion of this case have been included. Symmers (1948) drew attention to the association of myeloid leukæmia and Hodgkin's disease (and sarcoma), and similar cases have been reported by Skworzoff (1930), by Samwick, Cohn and Swiller (1955), and by Wilken (1957). Craver (1936) reported a case of monocytic leukæmia and Hodgkin's disease.

Krim *et alii* (1952) reported a case of conversion of aleukæmic lymphatic leukæmia to Hodgkin's disease and pointed out that this particular variant was not included in the Custer diagram. Gill and McCall (1943), in reporting a case of Hodgkin's disease terminating with the hæmatological and clinical findings of acute lymphatic leukæmia, drew attention to the occasional finding of leucocytosis in lymphadenoma, and suggested that histological evidence was required to substantiate the diagnosis of leukæmia in the presence of lymphadenoma. Seife, Reich and Zisa (1951) reported a further case of chronic lymphatic leukæmia, in which the predominant histological lesions at autopsy were those of Hodgkin's disease, with some leukæmic deposits in the bone marrow and liver. The return to normal of the leukocyte count in the terminal phases of this case parallels the fall in our own. A possible explanation lies in the replacement of the lymphatic tissue by the second tumour. Warfield and Kristjanson (1916), McMahon and Parker (1930) and Watson (1938) have also reported the association of Hodgkin's disease with lymphatic leukæmia. The above-mentioned reported cases cover a number of interconversions closely related to that of our case, but on critical examination none of them corresponds exactly to both types of tumour. Richter (1928) reported a case of reticulum cell sarcoma associated with lymphatic leukæmia in which the histological findings resembled those in our case. They stated that the tumour cells, although intimately intermingled, were morphologically distinct, that there was no evidence of transition of the cells of one lesion into the other, and that complete independence of the lesions was conceivable, but not susceptible of direct proof. Epstein (1956) reported a case of chronic lymphatic leukæmia terminating as Hodgkin's disease (sarcoma) in which the duration of the disease was seven years. This case also closely

resembled ours histologically. The leucocyte count was 17,000 per cubic millimetre, with 70% lymphocytes, and the first diagnosis was based on the bone marrow findings and lymph node biopsy.

Robb-Smith (1947) gives the incidence of lymphatic leukæmia as 36·3 per million and of lymphoid reticuloses as 49 per million in Oxfordshire, and though the possibility of coincidental development appears unlikely, it cannot be excluded.

In addition to the foregoing findings, this case presents several unusual clinical features. The cessation of accelerated hæmolysis of the red cells after splenectomy is consistent with the findings of Fisher and Welch (1952), who reported a series of cases of splenectomy in leukæmia and leukosarcoma, and included amongst their indications for splenectomy the presence of excessive hæmolysis.

The long history of recurrent infection is of interest in view of the finding of a low serum gamma globulin content. Jim and Reinhard (1956) and Jim (1957) investigated 50 cases of chronic lymphatic leukæmia and found hypogammaglobulinæmia in one-third. In their cases there was no coexistent history of recurrent infections. They attributed the changes in gamma globulin levels to the disturbance of the reticulo-endothelial system.

Summary.

A case is presented which commenced as one of typical clinical lymphatic leukæmia, confirmed by hæmatological findings, marrow examination and histological examination of the spleen after splenectomy. The patient's condition improved after treatment, but he died five years after first diagnosis, and at autopsy extensive histological changes of reticulum cell sarcoma were found in the organs in addition to less prominent leukæmic infiltrates. The interchange of types amongst the reticuloses is briefly discussed, with particular reference to lymphatic leukæmia. We have found only two cases in the literature which correspond to the change found in this case.

Acknowledgements.

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Legends to Illustrations.

FIGURE II.—Spleen removed at operation, showing uniform lymphoid infiltration. (Hæmatoxylin and eosin, × 90.)

FIGURE III.—Liver at autopsy, showing pure lymphoid infiltration around a portal tract. (Hæmatoxylin and eosin, × 180.)

FIGURE IV.—Liver at autopsy, showing mixed lymphoid and reticulum-cell infiltration. (Hæmatoxylin and eosin, × 250.)

FIGURE V.—Liver at autopsy, showing a reticulum-cell deposit. Pleomorphic and multinucleated cells are evident. (Hæmatoxylin and eosin, × 250.)

FIGURE VI.—Marrow at autopsy, showing multinucleated reticulum cells, resembling Sternberg Reed cells. (Hæmatoxylin and eosin, × 1250.)

IDIOPATHIC HYPERCALCÆMIA OF INFANCY IN AUSTRALIA.

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IDIOPATHIC HYPERCALCÆMIA of infancy was described first by Lightwood in England in 1952, and since then many papers reporting this disorder have appeared from all parts of the British Isles. Not long after the first description, it was recognized in Europe (Fanconi, Girardet, Schlesinger, Butler and Black, 1952), and within a few years had been reported from most continental countries. It was not until 1954, however, that it was reported from America (Deutch and Senturia, 1954), and even now it is considered sufficiently uncommon there for single cases to be presented. No report of this condition has yet come from Australia.

By now the clinical features of this illness are well known: its onset in infancy, the vomiting, failure to thrive, constipation, irritability, thirst and polyuria; in the severe cases, the typical facial appearance, mental deficiency, cardiac murmur, hypertension, bone changes and renal damage.

The purpose of this paper is to record four cases of idiopathic hypercalcæmia of infancy which have been identified in Perth in the past three years. One of these children died at the age of three years, two have been followed for two years under treatment and the last has been followed for one year. Three of the children had the disease in a severe form, and the fourth in a mild form.

This paper is presented mainly to emphasize the occurrence of this disorder in Australia. It is hoped that, by recording its geographical incidence, some contribution to the ætiology may be made.

Case I.

The patient was a male, born on December 2, 1954. He was a full-term baby, the third in the family, the other two being healthy. His birth weight was 5 lb. 12 oz. He was breast fed for three weeks, then put on an artificial feeding because his mother developed a breast abscess. For a few weeks he thrived, but then he became difficult with feeds and failed to gain weight.

He was admitted to the Princess Margaret Hospital, Perth, at the age of nine weeks, and was found to have a systolic murmur in his heart. During seven weeks in hospital he had an intermittent pyrexia for which no cause was found.

His subsequent progress was very slow. He developed obstinate constipation, and his mental development was grossly retarded. He continued to have bouts of fever, particularly in hot weather, and it was noted that, although he disliked milk, he was eager for water. From three to nine weeks he was given "Glaxo No. 1" with 10 drops of

FIGURE I.
Case I: characteristic facies of idiopathic hypercalcæmia.

"Pentavite". This represented an estimated total of 1200 units of vitamin D per day. From nine weeks to eleven months he was fed on cow's milk with lactone syrup, solids and "Pentavite"—approximately 400 units of vitamin D per day. From 11 to 17 months he received a normal diet with no added vitamin D.

On his readmission to hospital at 17 months he was pale, uninterested and grossly undernourished, his weight being 13 lb. Marked generalized hypotonia was present and he was unable to sit up or hold his head up. His forehead was prominent, and he had an unturned nose, a large mouth and and a receding chin with rather low-slung ears (Figures I and II). There was a loud systolic murmur in his heart, and the blood pressure was 170 mm. of mercury measured by the flush method. The diagnosis was suggested by the facial appearance and confirmed by investigations, which gave the following results. The serum calcium and phosphorus contents were 14 and 8 mg. per 100 ml. respectively. The serum chloride content was 103 mEq/l., the carbon-dioxide combining power was 25 mEq/l., the blood urea content was 110 mg. per 100 ml. and the erythrocyte sedimentation rate was 95 mm. in the first hour. Radiological examination showed findings characteristic of idiopathic hypercalcæmia of infancy (Figure III). The shafts of both femora and tibiæ were sclerotic, and there were lines of interrupted growth in the metaphyses. The distal metaphyses of the femora showed band-like zones of increased density, and the lower femoral and upper tibial epiphyses showed concentric rings of sclerosis.

He was given cortisone in a dose of 75 mg. per 100 ml., and this caused a fall in the serum calcium content to 11·9 mg. per 100 ml., and a clinical improvement. However, this improvement was not maintained, and there was never any change in his mental state. The cortisone was stopped after nine months. The systolic murmur disappeared when he was two years old.

The child eventually died in the Claremont Mental Hospital at the age of three years. No post-mortem examination was obtained.

Case II.

The patient was a female, born on December 28, 1955, at full term; her birth weight was only 4 lb. 3 oz. She was initially breast fed, but then numerous feeding changes

FIGURE II.
Case I: full face.

were made because of a slow weight gain. At four months she weighed 9 lb. At eight months she started vomiting, mainly solid food. Her motions were hard, but not infrequent. Her milestones of development were rather slow; she sat up at 10 months and could only just stand with support at 13 months. She was not unduly thirsty, and no urinary symptoms were noticed. From birth to three months she was fed on expressed breast milk with no added vitamin D. From three to four months she was given "Lactogen" and "Pentavite", with an estimated daily total of 800 units of vitamin D. From four to thirteen months she was fed on cow's milk, "Ideal Milk" and "Carnation Milk" and "Pentavite", with an average daily intake of about 500 units of vitamin D.

The child was admitted to the Princess Margaret Hospital at 13 months. Examination showed her to be a grossly undernourished baby weighing 13 lb. She had the typical appearance of infants with idiopathic hypercalcæmia — a small head (circumference 16·5 in.), a

receding chin, a large mouth, and poorly formed, widely separated teeth (Figures IV and V). There was marked generalized hypotonia. No systolic murmur was heard. The blood pressure was 120/80 mm. of mercury.

A number of investigations were carried out. The serum calcium, phosphorus and cholesterol contents were 15·6, 6·2 and 238 mg. per 100 ml. respectively. The blood urea content was 60 mg. per 100 ml. Radiological examination of the long bones showed a slight increase in density at the distal ends.

Cortisone was given in a dose of 50 mg. per day, and changed after one month to prednisone, 10 mg. per day. With this treatment there occurred an improvement in appetite, a fall in the serum calcium level to 12·2 mg. per 100 ml. and a gain in weight of 3 lb. in two months. The cortisone resulted in a "moon-face" appearance. After eight months' treatment prednisone was stopped, and a diet of low calcium content was started with "Locasol" ("Trufood") and a cereal of low calcium content ("Glaxo"). The weight gain was steady but slow, and at three years the patient weighed only 26 lb.

Her serum calcium level has been consistently below 12·0 mg. per 100 ml. since the first week of treatment, and the blood urea content has been normal. At two years and nine months, after 18 months of treatment, milk was introduced slowly, and by the age of three years she was having a normal diet. There was no increase in serum calcium content when this was done. Her milestones of development have been reached slowly, but she has made a gradual progressive improvement. At the age of two and a half years she started walking, and at three and a half years she uses little phrases. Her skull circumference is 18 in.

Case III.

The patient was a female, born on January 19, 1958, at full term, the birth weight being 6 lb. 12 oz. One other child, aged seven years, is well. Her progress was normal for ten weeks, but then she developed a respiratory infection, after which she commenced vomiting, became anorexic and constipated and began to lose weight. Her activity was normal and she was quite a happy baby. At five months, when a diagnosis of idiopathic hypercalcæmia of infancy was made, she was reaching for objects and was making gooing noises. She was breast fed for one month, and from two to five months she was fed on "Glaxo No. 2", her diet containing approximately 1000 units of vitamin D per day.

She was admitted to the Princess Margaret Hospital, and on examination she was found to be wasted and sunken-eyed. Her weight was 9 lb. 2 oz. No cardiac murmur was heard, and her systolic blood pressure was 130 mm. of mercury by the flush method. The skull circumference was 15·5 in. A number of investigations were carried out. The serum calcium and phosphorus contents were 15·9 and 3·3 mg. per 100 ml. respectively. The serum alkaline phosphatase content was 8·5 King-Armstrong units. The blood urea content was 46 mg. per 100 ml. Microscopic examination of the urine revealed 17 leucocytes and five erythrocytes per high-power field of the centrifuged deposit. The radiological findings in the long bones were normal.

Treatment was started at the age of five months with prednisone and a diet of low calcium content. The serum calcium level fell to 10·5 mg. per 100 ml. in three weeks, and there was a coincidental weight gain. The prednisone was gradually reduced and was stopped completely at the age of 10 months.

The introduction of cow's milk was begun at this stage, and a full diet was being taken at 12 months. Her weight gain has been rather slow, and at 18 months she weighs 19 lb. 3 oz. She started walking at 17 months and says several words.

Case IV.

The patient was a male, born on December 20, 1958, at full term, the birth weight being 5 lb. 6 oz. His progress in the first three months whilst breast fed was satisfactory, but after this his weight gain was slow, and at

FIGURE III.

Case I: radiograph of lower limbs, showing characteristic transverse lines of interrupted bone growth in the femora and tibiæ, the dense metaphyses, and ring-like densities in the epiphyses.

six months he developed a paroxysmal cough which was associated with vomiting. The cough gradually subsided, but he continued to vomit, mainly with solid food, which he was persuaded to take with great difficulty. He drank milk well and was keen for extra water. At nine months a systolic murmur was heard in his heart, and an electrocardiogram showed evidence of right bundle branch block. He was not constipated at any time. His mental development was delayed, and he made no attempt to crawl at 11 months. From birth to three months he was breast fed. From three to six months he was given "Glaxo No. 2" and 12 drops of "Pentavite", a diet containing approximately

FIGURE IV.
Case II: characteristic facies of idiopathic hypercalcæmia.

1400 units of vitamin D per day. From six to nine months he was given "Lactogen" *plus* 12 drops of "Pentavite" per day. This represented a daily intake of 800 units of vitamin D.

On examination, the baby was seen to be small, his weight being 13 lb., and he had the typical facial appearance of hypercalcæmia. He was rather pale, and his muscle tone was poor. There was a systolic thrill in the chest, with a loud systolic murmur in the precordial region. The second sound was rather widely split. The blood pressure was 120/80 mm. of mercury in the right arm. He appeared to be quite happy and responded normally to stimulation.

A number of investigations were undertaken. The serum calcium, phosphorus and cholesterol contents were 13·9, 8·0 and 200 mg. per 100 ml. respectively. The blood urea content was 71 mg. per 100 ml. Radiological examination revealed increased density of the cortex of the calvarium and the floor of the anterior fossa.

He was given prednisolone in an initial dosage of 20 mg. per day and a diet of low calcium content. His serum calcium content fell to 10·5 mg. per 100 ml. after two weeks of treatment. He has taken his food more eagerly since treatment was started, and appears to be brighter. There had been no improvement in weight up to January 18, 1960.

It is difficult to be sure whether the systolic murmur and the right bundle branch block indicate a congenital abnormality, or whether they are simply part of the hypercalcæmia.

Laboratory Methods.

The earlier serum calcium estimations, before June, 1958, were made by the procedure of Clark and Collip (1926) as described by King and Wootton (1956). After that date the analyses were carried out by a modified method of Wilkinson (1957), using 0·1 ml. of serum.

Bicarbonate was estimated by the capillary method of Wright and Colebrook (1921), modified by King (1947).

The blood urea content was estimated by the urease and nesslerization method (King and Wootton, 1956). The

FIGURE V.
Case II: characteristic facies of idiopathic hypercalcæmia.

serum alkaline phosphatase content was estimated by the modified method of King and Armstrong (King, 1947).

The serum phosphorus content was estimated by the micro method, 0·2 ml. of serum being used (King, 1947).

The serum cholesterol content was estimated by the method of MacIntyre and Ralston (1954), a modified Liebermann-Burchard reaction being utilized.

Discussion.

The diagnosis of idiopathic hypercalcæmia of infancy in these four cases was confirmed by biochemical analyses.

The infants in Cases I, II and IV, whose histories are described, can be classified as suffering from severe idiopathic hypercalcæmia; all three had mental retardation and typical facial appearance. A slight excess of vitamin D was given to the first, third and fourth infants, but not to the second infant. It is worthy of note that all the severely affected infants were of low birth weight despite a normal gestation period. These cases are similar in all respects to those described elsewhere, and the last three patients have had a satisfactory response to cortisone and a diet of low calcium content. Like other reported cases, the weight gain has been below average despite maintenance of a normal calcium level.

The geographical incidence of idiopathic hypercalcæmia of infancy is very unusual. It is common in Britain and Europe, but rare in America, and the present report is the

first to come from Australia. It is unlikely that after seven years the frequency of the condition in the United Kingdom is entirely due to a greater awareness of the condition. Other explanations suggested are an excessive intake of vitamin D (British Pædiatric Association Report, 1956) and the high proportion of dried-milk feeding in the United Kingdom. The role of vitamin D has not yet been fully elucidated; but if it is a factor, and it certainly seems to be, it is not due to overdosage in every case. In some cases in which excessive vitamin D has not been given, one must postulate an idiosyncrasy or an excessive reaction to this vitamin (Stapleton, Macdonald and Lightwood, 1957).

The proponents of the dried-milk theory have pointed out that idiopathic hypercalcæmia of infancy is rare in America, where the majority of artificial feeds are made up with evaporated milk (Sinclair, 1956*a*). It has been stated that dried milk contains a smaller proportion of essential fatty acids which are important in sterol metabolism (Sinclair, 1956*b*). Analysis of the fat composition of milk has shown that the essential fatty acid content of dried milk is equal to that of fresh cow's milk, but that it decreases after storage (James, Webb, Stapleton and Macdonald, 1958). In this regard it is notable that about 60% of infants in Western Australia are breast fed during the first few months of life, and of those babies fed artificially, about half are given dried milk, one-third fresh cow's milk and one-sixth evaporated milk (Gibson, personal communication).

In the four cases described in this report, all the patients were given dried milk as the first artificial feed; but four cases only are of no significance.

Summary.

1. Four cases of idiopathic hypercalcæmia of infancy are reported.

2. This is the first report of this disease in Australia.

3. The geographical distribution of the disease and its relation to ætiology are discussed.

Acknowledgements.

I should like to express my appreciation to Professor W. B. Macdonald for criticism and for help in writing this article, and to my colleagues at the Princess Margaret Hospital, Perth, for permission to report the histories of patients under their care.

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RETAINED PRODUCTS OF CONCEPTION.

By ROBERT F. ZACHARIN, F.R.C.S., F.R.A.C.S., M.R.C.O.G.,
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IN gynæcological practice, retained products of conception must be considered in a differential diagnosis. The modes of presentation vary from the common incomplete abortion, to placental polypi and post-abortional pelvic inflammatory diseases. Often difficulties in diagnosis are met by the simulation of ectopic pregnancy, or of organic pelvic disease.

The cases to be reported are unusual, but display the extreme variety of presentation which may occur. The first illustrates the importance of considering retained products of conception in a differential diagnosis. The second shows the difficulty which can be met, when pregnancy does not seem to be a relevant consideration.

Case I.

Mrs. A., aged 24 years, presented in September, 1958, complaining of persistent vaginal discharge, present for six months, worse before her menstrual loss, but never irritating. Dyspareunia was the only relevant symptom. Approximately six months before, when about 12 weeks pregnant, she had miscarried. She had been admitted to hospital, but with the cessation of the bleeding, curettage was waived. Since that abortion, her menstrual cycle had been completely normal. She had three children, the youngest of whom was aged 18 months. The discharge had been treated with a wide variety of vaginal suppositories. At no stage had a speculum examination been made.

The only positive finding was obtained on speculum examination. Darkened, hard, irregular, bony structures were embedded in a mass of juicy red granulation tissue at the external os. Under anæsthesia and a chemotherapy "umbrella", several fœtal skull bones were freed from the cervix (Figure I). There were minimal uterine scrapings.

Two months later, at review, the discharge had ceased and the cervix was normal.

Comments are self-evident. The ætiology of the discharge had not been established before previous treatment was given. Once the cause was realized, simple treatment was effective.

Case II.

Mrs. B., aged 30 years, was examined in consultation on December 28, 1958. She complained of sudden onset of severe and continuous pain in the left iliac fossa, and in the lower part of the back. The December menstrual period was on time, and had begun concurrently with the pain; but the character of the loss differed markedly from normal. Eighteen months before, she had had three abnormal menses, the interval being grossly irregular and the loss much less than usual. After that incident, menstruation was regular and the amount of loss normal. Twelve months prior to the consultation a Graffenburg ring had been inserted, but removed six months later because of menorrhagia. Menstruation again returned to normal with its removal. One month prior to the consultation, whilst the patient was engaged in heavy lifting, a sudden severe pain occurred in the left iliac fossa, exactly similar to the present attack, but vanished completely after several hours. There were no other symptoms, and its cessation was accompanied by the beginning of a normal menstrual period. The patient had one child, aged six and a half years; pregnancy and delivery had been normal.

Examination of the patient showed her to have a temperature of 38·6° C. and a pulse rate of 120 per minute. A mass which could be seen arising from the left iliac fossa distended the abdomen. Palpation demonstrated its exquisite tenderness, irregularity and fixity. The menstrual discharge resembled altered blood clot and

pus. Pelvic examination under anæsthesia after the passage of a catheter showed a large irregular mass in the left lateral and posterior fornices, closely related to the uterus, but separate from it and continuous with the abdominal swelling. It was thought probably to be confined by the broad ligament. The uterus was displaced to the right, yet the right lateral fornix appeared normal.

Before operation a definite diagnosis was not made; but infection of a broad ligament cyst was considered.

Abdominal exploration revealed a grossly distended left broad ligament. Both Fallopian tubes and ovaries were normal. Both round ligaments had normal relationships to the uterine cornua. The uterus was soft and a little larger than normal. Division of the left round ligament released pus and altered blood. Exploration of the cavity

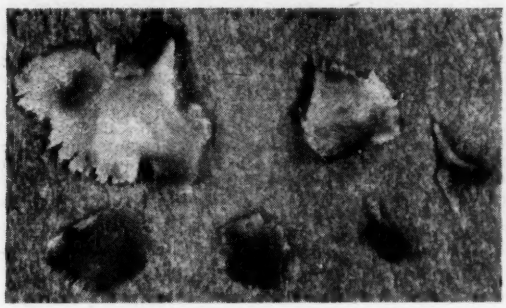

FIGURE I.

showed several features. Macerated fœtal and placental remains were found. A finger could be passed through a ragged hole, and then either into a smooth uterine cavity or out through the cervix into the vagina. Abdominal and vaginal drain tubes were inserted into the abscess cavity and the abdomen was closed.

Convalescence was uneventful, and at review on February 13, 1959, the patient was well. There was much thickening in the site of the former abscess, and the uterus was displaced to the left. The discharge had ceased.

On February 18 a report on a hysterosalpingogram (Figure II) read as follows:

> The cervix is drawn over to the left causing slight distortion of the cervical canal and suggesting adhesions in the broad ligament on the left side. The uterine cavity is normal in size and shape and the opaque media flowed freely down both Fallopian tubes, which are also normal in appearance. Free spill occurred into the peritoneal cavity and the opaque medium seen on both sides of the pelvis is probably due to spill through the Fallopian tubes. No sinus or cavity connected with the uterus was demonstrated, but it is possible that there could be a fistula connected with the cervix and responsible for some of the opaque media on the left side.

A pathological examination of the removed fœtus and placenta was made. Macroscopic examination showed the fœtus to be 9 cm. in length; advanced maceration was seen in the greater part. Portions of placenta were present. The report on the microscopic examination was as follows:

> Sections through the blood clot and placental tissue show that the villi in the latter are very markedly fibrotic and that only some are surrounded by a thin rim of hæmatoxiyin staining trophoblast cells. There are no other significant microscopic findings.

Comment.

The explanation of this broad ligament pregnancy is difficult.

The duration of gestation can be established from the fœtal length, and the degree of maceration suggests its retention for at least 12 months. The possibilities of its evolution may be summarized as follows: (i) tubal pregnancy; (ii) primary abdominal pregnancy; (iii) pregnancy in a rudimentary horn; (iv) pregnancy in a uterine sacculation or diverticulum; (v) the result of uterine trauma.

Both Fallopian tubes were normal, the peritoneal surface of the broad ligament was intact and the round ligaments showed normal attachments to the uterine cornua. Therefore the first three possibilities can be dismissed.

Uterine sacculation does occur. It may be abnormal or physiological. The former type is thought due to excessive trophoblastic activity at the time of imbedding (Rubovits, 1951). In such reported cases, uterine muscle surrounding

FIGURE II.

the sac and connected to the pregnant uterus by a small aperture is described. Clinical presentation is late in pregnancy. The site may be mid-line, lateral or in relation to a utero-tubal orifice. Evidence of abnormal Müllerian fusion is not a prerequisite.

The physiological sacculations referred to by Palmer are no help in elucidating this case. Possibly this was a pregnancy in a low lateral sacculation, although it shows striking differences from previously reported cases.

The most likely explanation of this "cervical fistula" is uterine trauma. The manipulations employed with the Graffenburg ring could supply the answer.

Acknowledgements.

Dr. Robert Barter, Assistant Director of Pathology at the Royal Women's Hospital, Melbourne, prepared the pathological report in Case II and contributed to the elucidation of this case. Mr. R. Inglis, clinial photographer at Royal Melbourne Hospital, prepared the photographs.

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Reviews.

Growth Diagnosis: Selected Methods for Interpreting and Predicting Physical Development from One Year to Maturity. By Liona M. Bayer and Nancy Bayley; 1959. Illinois: The University of Chicago Press. 11" × 8½", pp. 256, with 171 illustrations and many tables. Price: $10.00.

THIS is a rather elaborate production, which describes the various techniques that can be used to measure growth and demonstrates how these techniques can be employed to make or confirm the diagnosis of a number of diseases and conditions. The techniques recommended include the usual anthropometry of weight and stature, and three other

body measurements which the authors consider to be reliable in the clinical evaluation of growth—namely, trunk length, biacromial diameter and bicristal diameter. Photographs of the whole body, taken under standard conditions, and a radiograph of the wrist to determine skeletal age are also recommended. Then follows a section devoted to the changes in measurement and body configuration with age; these are extensively illustrated from the clinical material of the authors. Differences in the male and the female body forms are shown with a series of elaborate illustrations and graphs, and interesting among these photographs are bisexual forms of both the male and female.

The larger portion of the book is devoted to examples of departures from the normal—namely, early and late maturation in children and a variety of diseases, such as obesity, female castration, the hypogonadal male and female pseudo-hermaphroditism. Extensive charts, diagrams and illustrations are given for each of these diseases and conditions.

The contents of this book emphasize the interest in the longitudinal study of children that has been a feature of a number of child study centres during the last 25 years. These studies have undoubtedly contributed much to our knowledge of growth and to the physical characteristics of certain diseases. This publication summarizes technical procedures and indicates the usefulness of information that can be collected in this way.

This book should have a place on the library shelves of any teaching institution or hospital which caters for children, since its illustrations would be of considerable value in helping to confirm a provisional diagnosis in which growth is affected. However, it is doubtful whether more than a handful of pædiatricians and general practitioners interested in children would find this book of great value, although they undoubtedly would find in it much of interest to them.

High Blood Pressure and Pregnancy. By Lance Townsend, M.D., B.S., F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G., D.T.M. & H.; 1959. Victoria: Melbourne University Press. 8½" × 5½", pp. 124, with 26 tables. Price: 40s.

PROFFESSOR TOWNSEND has made a brave attempt to compare the incidence and effects of a raised diastolic blood pressure on both mother and fœtus between two groups of women admitted to the Royal Women's Hospital, Melbourne, during the years 1946-1947 and 1956. As the lower limit of "high" blood pressure, he has chosen to use the figures accepted by the Metropolitan Life Assurance Co., which in the upper parturient decades reach 140/90 mm. of mercury. This level of definition must be repeated at least twice, and must be observed before the twentieth week of pregnancy. Patients with known renal hypertension were wholly excluded. In 1946, 111 patients satisfied the criteria (1·3% of all admissions), and in 1956, 109 patients (1·6% of all admissions).

The contrast in treatment was considerable. In the older group, blood pressures were obtained by many observers, who at the time were more interested in the systolic reading. The patients were mainly out-patients; ante-natal care was irregular, and no particular diet was advised. The appearance of proteinuria usually led to admission to hospital and termination of pregnancy. This dark era had disappeared by 1956, when a thorough physical examination, and ready admission to hospital were introduced, with rest, dietetic measures and reserpine therapy in a dosage of 0·25 mg. three times a day. Blood pressures were recorded in a consistent and approved method by the author. The good lessons taught by the staff of the Women's Hospital, Crown Street, Sydney, were followed in all pregnancies, where attention was paid to weight gain, and to sodium and protein intake. Pentolinium tartrate was employed if the above-mentioned measures were ineffective, but fortunately in quite small doses. If the blood pressure continued above 150/90 mm. of mercury, the patient was admitted to hospital. If proteinuria then appeared, or failed to disappear, from a catheter specimen of urine, or if a relative rise of 10 mm. or more in the diastolic pressure or œdema occurred, therapeutic abortion was considered. Every attempt was made to carry the patient on to the thirty-seventh week. Nineteen pregnancies were terminated in the 1946 series, but only eight in the 1956 group. There were no maternal deaths in 1956, and one in 1946. Age and parity were found to have no significance. The perinatal fœtal mortality in 1956 was eight, or four times that in all booked patients at the Royal Women's Hospital, while in 1946 it was ten. In the older group this bore no relationship to the initial diastolic pressure in the mother, but in the more recent series, the mortality rose in step with the initial diastolic pressure. Accidental hæmorrhage was not seen at all in the latter group. Other conclusions reached by the author as a result of his study are that present-day management of pregnancy hypertension reduce blood pressure at the end of the pregnancy, reduce proteinuria, reduce prematurity and fœtal wastage and increase fœtal size. He recommends rupture of the membranes if the blood pressure is rising at the end of 37 weeks, and quotes 5% as an attainable target of fœtal loss if the methods outlined are followed.

The book is by no means easy to read; it is repetitious, and comparisons between the two groups are largely invalid, as there are so many variables uncontrolled in such retrospective studies. Percentages are used with irritating frequency in a statistically unacceptable context. The author is conscious of these criticisms, and it to be congratulated on having gained the utmost, if not more, from his material. The analysis is very complete. The author is to be commended for his attitude to the vexed question of standards for pregnancy hypertension, for his insistence on the diastolic blood pressure being kept below 90 mm. of mercury and on the readings being taken by a single experienced practitioner (not a nurse), on the importance of proteinuria and on a relative rise in blood pressure being more important than any arbitrary level. We congratulate him on his detailed and logical approach to an elusive and prickly problem, and on his good results. We wish we could share his faith in the efficacy of the ganglion-blocking drugs, which in our view, are not without danger to the fœtus. In spite of its weaknesses, this is an important addition to Australian obstetric literature.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Is Sex Necessary?", by James Thurber and E. B. White; 1960. Mitcham, Victoria: Penguin Books in association with Hamish Hamilton. 7" × 4¼", pp. 144 with illustrations. Price: 4s.

"Homosexuality", by D. J. West; 1960. Mitcham, Victoria: Penguin Books. 7¼" × 4¼", pp. 200. Price: 5s. 6d.

"The Clinical Application of Antibiotics: Erythromycin and other Antibotics", by M. E. Florey, M.D.; Volume IV; 1960. London, New York and Toronto: Oxford University Press. 9¾" × 6", pp. 312. Price: 121s.

"Predisposition to Postvaccinial Encephalitis: Significance of Constitution, Especially the Status Dysraphicus in the Genesis of Postvaccinial Encephalitis", by E. J. W. Keuter; 1960. Amsterdam, London, New York and Princeton: Elsevier Publishing Company. 8¾" × 5¾", pp. 168, with many illustrations and tables. Price: 46s. (English).

"Annual Review of Physiology", edited by Victor E. Hall with the assistance of Frederick A. Fuhrman and Arthur C. Giese; Volume 22; 1960. Palo Alto, California: Annual Reviews, Inc. and the American Physiological Society. 8¾" × 5¾", pp. 738; Price: $7.00.

"International Work in Leprosy 1948-1959", reprint from WHO Chronicle, Volume 14, No. 1, 1960. Geneva: World Health Organization. 9½" × 7¼", pp. 40, with many illustrations. Price: 1s. 9d.

"Expert Committee on Leprosy: Second Report", World Health Organization, Technical Report Series, No. 189; 1960. Geneva: World Health Organization. 9½" × 6¼", pp. 28. Price: 1s. 9d.

"Epidemiology of Cancer of the Lung: Report of a Study Group", World Health Organization, Technical Report Series, No. 192; 1960. Geneva: World Health Organization. 9½" × 6¼", pp. 16. Price: 1s. 9d.

"Epidemiology of Mental Disorders: Eighth Report of the Expert Committee on Mental Health", World Health Organization, Technical Report Series, No. 185; 1960. Geneva: World Health Organization. 9½" × 6¼", pp. 32. Price: 1s. 9d.

"Growing up in Newcastle upon Tyne: A Continuing Study of Health and Illness in Young Children within their Families", by F. J. W. Miller, S. D. M. Court, W. S. Walton and E. G. Knox; 1960. London, New York, Toronto: The Nuffield Foundation, published by the Oxford University Press. 8½" × 5½", pp. 398, with many tables and illustrations. Price: 46s. 6d.

"Notes on Infant Feeding", by Stanley Graham, LL.D., M.D., F.R.C.P. (Ed.), F.R.F.P.S. (Glas.), and Robert A. Shanks, M.D., M.R.C.P. (Lond.), F.R.F.P.S. (Glas.); Fifth Edition; 1960. Edinburgh and London: E. & S. Livingstone Ltd. 7¼" × 4½", pp. 76. Price: 4s. 6d. net (English).

The Medical Journal of Australia

SATURDAY, JULY 23, 1960.

THE MEDICAL SCHOOL OF THE UNIVERSITY OF NEW SOUTH WALES.

THE Medical School of the University of New South Wales, the second medical school in the State, is well under way. Appointments were made to its five foundation chairs some time ago, and it began to take material shape on Monday, July 4, 1960, when the State Premier, the Honorable R. J. Heffron, set the foundation stone for its first building. Sited on the high ground above the parent University, two buildings are planned. The first is to be a large building of seven floors, 353 feet in length and estimated to cost one and a half million pounds. This will house the first-year medical biological sciences, the school of biochemistry and the University's non-medical biological science activity. The second building of the group is to accommodate the pre-clinical facilities for the schools of anatomy, pathology and physiology. It will be a building of six floors at right angles to the first building and connected with it. The project includes a group of five lecture theatres conveniently located to all departments.

It has been announced, and the Premier referred to this in his speech, that students who intend to study medicine at the University of New South Wales will be enrolled in March, 1961, but during the first year they will take the same courses in physics, chemistry, mathematics and general biology as their fellow students in science. The course will be of six years' duration and is being designed to satisfy the full requirements of the General Medical Council. It is interesting to note, and commendable, that the policy of the University of New South Wales of including studies in the humanities in all courses will be followed in the medical course. The projected new buildings are designed for a maximum intake of 200 students, and it is stated that they will be ready for them by March, 1962. No official announcement has been made, so far as we know, on whether it is intended to restrict the numbers to 200 by means of a firm quota system or if there is any possibility of complete freedom of enrolment of all matriculants as in the University of Sydney. Uniformity of policy in this regard would seem to be desirable. Information on this and on other aspects of the medical course will be awaited with genuine interest.

None of those who braved the biting wind of a winter afternoon to join the Premier in the ceremonial act of initiation of this new medical school could do other than wish it well. If there were any hatchets still in circulation, we may hope that they were firmly entombed behind the foundation stone. All who have the interests of good medicine at heart must do what lies in their power to see that the school is as good as it can be, and that those who have charge of it are given every encouragement. Adequate buildings have been promised, serious attention is being paid to the provision of teaching hospital facilities, and the curriculum is being planned with care. A first-class team of men occupy the foundation chairs. Three graduated from the University of Sydney—the Dean of the School and Professor of Surgery, Francis Felix Rundle, the Professor of Medicine, Ralph Beattie Blacket, and the Professor of Physiology, Paul Ivan Korner. Two come to us from elsewhere—the Professor of Pathology, Donald Lancelot Wilhelm, from Adelaide, and the Professor of Anatomy, Michael John Blunt, from London. They may be assured of the good will and confidence of their colleagues, who have as a whole a deep personal concern for the development of medicine in our country that is sometimes, without malice but nonetheless unfortunately, not appreciated by those in authority.

After the ceremony of setting the foundation stone, the Chancellor of the University of New South Wales, Dr. Wallace C. Wurth, conferred the degree of Doctor of Science, *honoris causa*, on the Honourable William Francis Sheehan, State Minister for Health. After receiving this honorary degree, the Minister, in a short and happy speech characteristically free from platitudes, mentioned among other things his opinion that there was room for two more medical schools in New South Wales. In view of the rapid development that is taking place now and that may be anticipated in the future, this seems a realistic view. It is to be hoped that in the planning of these future schools, serious notice will be taken of the report of the New South Wales Branch of the British Medical Association on this subject. This is an informed and conscientiously considered document, containing a wealth of relevant factual material, and nothing else of its kind is available. It does not present a sectional point of view in any unfortunate sense and is intended only to be constructive. We commend it earnestly to the State Government and its advisers, as well as to the universities.

TRACHOMA VIRUS.

WITH the decline in the incidence of the great pestilences —smallpox, typhus, cholera, yellow fever and plague— increasing attention has been turned to less dramatic but perhaps more pernicious diseases like malaria, yaws and trachoma, which cause much disability over a large part of the world. Of these only trachoma is of much importance in Australia, and we have recently described progress in the recognition and treatment of trachoma in Morocco[1] and Australia.[2] In the latter article brief mention was made of the recovery of trachoma virus from a case by Dr. Dorothy Perret, in the University of Western Australia.

Trachoma was shown to be caused by a filterable agent in 1912 by Nicolle, Blaisot and Cuenod,[3] but scientific

[1] MED. J. AUST., 1960, 1: 983 (June 18).
[2] MED. J. AUST., 1960, 2: 25 (July 2).
[3] *C.R. Acad. Sci. (Paris)*, 1912, 155: 241.

investigations were hampered for many years by the failure of all attempts to cultivate this in tissue culture or in a convenient laboratory animal. This impasse was broken in 1957, when T'ang and his associates,[4] working in Peking, successfully passed the virus in eggs inoculated by the yolk sac route. Collier and Sowa in the United Kingdom,[5] Grayston and his associates at Taipeh in Formosa[6] and others elsewhere have confirmed T'ang's observations, and intensive experimental studies of trachoma virus are now in progress in several centres. The most advanced work reported so far comes from Grayston and his colleagues at Taipeh.[6]

After describing the isolation of several strains of trachoma virus by T'ang's method, the group in Formosa showed that the isolated virus caused trachoma in human volunteers, but failed to grow in experimental animals or in tissue culture, except for the yolk sac of the developing egg and the conjunctival sac of the monkey. In this they confirmed previous observations. Like T'ang, they found that in chick embryos trachoma virus was resistant to streptomycin and partially resistant to chloramphenicol, but highly sensitive to penicillin, sulphonamides and tetracycline. They were able to prepare an antigen from trachoma virus suspensions which reacted specifically with sera from patients infected with trachoma, whereas the crude antigen reacted also with antisera to the related viruses of psittacosis and lymphogranuloma venereum. Preliminary experiments also showed that trachoma patients reacted specifically to the intradermal injection of the purified antigen, although no reactions occurred with Frei skin test antigen. The antigen was used as a vaccine both in monkeys and in human beings. High titre CF antibody was produced, particularly after the inoculation of formalin-treated vaccine adsorbed to aluminium hydroxide. Protection tests, as well as field trials with the vaccine, are being carried out.

All this work gives promise that a more effective attack on trachoma may be possible in the near future. It is clear that serological testing will greatly improve the accuracy of diagnosis, but the possibility of effective vaccination is still uncertain. The experiments of Grayston and his colleagues showed that vaccination was safe, for even the intramuscular inoculation of active virus was innocuous. But there is a large gap between safety and prophylactic value, and with agents of this group vaccination has been disappointing. Also there are the two problems of strain variation in antigenic pattern, which may occur with trachoma (Bell, Synder and Murray[7]), and of ensuring that sufficient antibody is present on the superficial surface of the conjunctiva to protect against infection.

The agent which causes trachoma, like those of psittacosis and lymphogranuloma venereum, is still called a virus. Nowadays most virologists would exclude it from the viruses (Lwoff[8]), mainly because they believe that its basic mode of reproduction is like that of the rickettsiæ and bacteria rather than like that of the true viruses. Subsidiary reasons are the possession of both ribonucleic acid and deoxyribonucleic acid (the true viruses have one or the other, never both) and at least a few metabolic enzymes, which form the basis of the drug sensitivity of these agents. But old habits die hard, and it will probably be years before doctors talk of these agents as anything except viruses.

[4] *Chinese Med. J.*, 1957, 75: 429.
[5] *Lancet*, 1958, 1: 993.
[6] *J. Amer. med. Ass.*, 1960, 172: 1577.
[7] *Science*, 1959, 130: 626.
[8] *J. gen. Microbiol.*, 1957, 17: 239.

Current Comment.

MONKEY MALARIA AND ERADICATION CAMPAIGNS.

A RECENT DISCOVERY by medical research workers that malaria of lower monkeys can be transmitted to man has raised fears for the success of the world malaria eradication campaign. Such fears are unfounded according to a statement recently issued by the Malaria Eradication Division of the World Health Organization. This points out that it has long been known that the higher (anthropoid) apes had malaria, and that man might be susceptible to certain malaria parasites of apes. Opportunities for the transmission of malaria from apes to man are exceedingly rare, and the problem has therefore little practical importance. The lower monkeys are also naturally infected with several types of malaria, but these are not transmissible to man. Quite recently, however, laboratory research has shown that one of the malaria parasites of these monkeys can be transmitted to man by the bite of an anopheline mosquito which has fed on the monkey's blood. A "reservoir" of malaria in monkeys may conceivably therefore add to the difficulties of eradicating human malaria in certain countries in which monkeys live in close proximity to man. It is important, however, not to exaggerate the gravity of this situation, which is similar to that of diseases such as yellow fever, filariasis or rabies where wild-life reservoirs of infection exist. Ways will have to be found of overcoming the difficulty, just as ways were found to overcome other difficulties in malaria eradication campaigns, such as the resistance of certain mosquitoes to insecticides. Moreover, the monkey-malaria problem is likely to present itself only in a few areas of some countries of east Asia and perhaps South America, while the eradication campaigns will be unaffected elsewhere. Indeed, the new discovery is considered to be a cause for rejoicing rather than for concern. From the research point of view it is an advantage to be able to work with a malaria parasite which causes the disease in man but which can also be studied in monkeys. This may indeed open vast possibilities for experimental studies on new antimalarial drugs which may hasten the final conquest of malaria.

THE SURGICAL APPROACH TO ADVANCED CANCER OF THE BREAST.

THE continuing stream of articles and reports dealing with the treatment of patients with metastatic mammary carcinoma is perhaps evidence of our continued failure to cure the original condition in a large proportion of cases, but it also testifies to the great amount of thought and effort which is being put into helping these patients. Several different approaches exist by which much may be done to alleviate their suffering, and all of which may procure a temporary remission of symptoms in a proportion of cases. When the radical surgical assault on the endocrine system began, many must have questioned whether such desperate attempts to delay the terminal stages of incurable disease were really in the patient's interest. However, there is now no doubt that in a considerable proportion of properly selected cases a worthwhile remission of symptoms can be obtained, and there are always the occasional cases in which the disease is halted and becomes completely quiescent for several years. Bilateral oophorectomy for the treatment of advanced breast cancer was first carried out by G. T.

Beatson in 1896, and his success induced a number of others to follow his example. However, though marked improvement was noticed in the condition of some patients, a discouragingly high proportion showed no benefit, and the operation fell into disfavour (C. Huggins and L. Y. Dao[1]). It was supposed that the reason why oophorectomy gave only temporary relief was that the secretion of œstrogens by the adrenal glands in time compensated for the loss of the ovaries. However, till cortisone became available, extirpation of the adrenal glands was not possible. Huggins and Dao were among the first to report the results of combined bilateral adrenalectomy and oophorectomy in a substantial number of patients, and this operation is still widely practised. The first report of the successful use of this operation in Australia was by Kathleen Cuningham early in 1954.[2] Though the results were superior to those of oophorectomy alone, they were still very inconstant, and it was thought that failures and relapses might be due either to aberrant adrenal tissue, which could be controlled by removal of the pituitary gland, or possibly to some substance secreted by the pituitary itself; so removal of the pituitary gland was the next logical step. R. Luft and H. Olivecrona reported encouraging results in a series of cases in 1953, and in the same year the first hypophysectomy for breast cancer to be done at Guy's Hospital, London, was performed by M. A. Falconer.

In 1957, H. J. B. Atkins, of Guy's Hospital, and his colleagues[3] reported a series of 60 patients with advanced cancer of the breast, of whom 30 had been treated by bilateral adrenalectomy with oophorectomy, and 30 by hypophysectomy, the operation to be performed in any one case having been decided by a method of random selection. At this stage a comparison of the two groups favoured hypophysectomy, but the results were not conclusive. Atkins and his colleagues have now published a further report,[4] in which their series has been extended to include 149 patients, of whom 79 were subjected to adrenalectomy with oophorectomy, and 70 to hypophysectomy. All of these patients had previously undergone radical mastectomy, or were already suffering from generalized metastases when first seen. The great majority had already exhausted the possibilities of deep X-ray therapy and hormone treatment, though in the more recent part of the series there is a small group of patients selected for "early" endocrine operation.

The results to date have been very carefully analysed, and they show a decided bias in favour of hypophysectomy in regard to both short-term clinical improvement and mean survival time after operation. There were seven post-operative deaths in the adrenalectomy series, and three in the hypophysectomy series, but a majority of these deaths were due to causes unrelated to the operation; it should be noted that many of these patients were already gravely ill. In discussing the implications of their findings, Atkins and his colleagues point out that the two populations compared are heterogeneous for all sorts of factors, such as age, parity, relationship to climacteric, etc. Though randomization has secured as far as possible that the elements of heterogeneity are evenly distributed in the two populations, the possibility exists of the presence of important sub-groups which may be particularly suited to one form of treatment or another. Here we are faced with the familiar difficulty of finding series large enough to provide answers to more than one or two questions. In the long run many questions must await the results of widely-based cooperative trials such as that recently discussed in these columns.[5] A sufficient number of cases can never be assembled in one centre. However, the basic advantage of hypophysectomy in the majority of cases appears indisputable. Atkins and his colleagues then inquire whether this means that adrenalectomy should be abandoned in favour of hypophysectomy. Their discussion of this point should be read by anyone interested in the ethics of controlled trials. In the outcome, they have no difficulty in showing that because of the sheer magnitude of the problem in relation to the resources available, both operations must be persevered with. Otherwise patients who could benefit from adrenalectomy might die while waiting for hypophysectomy. In any case, though the difference in the results of a series is statistically significant, the outcome in any one case is quite uncertain.

This leads to the question of the selection of patients. Atkins and his colleagues were surprised to find that, contrary to what had been reported by some other workers, the response to previous hormone therapy seemed to give no indication as to which patients would be likely to benefit from endocrine surgery. However, a few groups can be defined. Atkins and his colleagues believe that patients with pulmonary metastases causing dyspnœa should not be subjected to adrenalectomy. In another paper published at the same time, R. D. Bulbrook, F. C. Greenwood and J. L. Hayward[6] set out the results of hormone assays of the urine of patients in the Guy's Hospital series. Out of a large number of estimations, they found only two which appeared to have any prognostic value, namely the ætiocholanolone and 17-hydroxycorticosteroid levels. In the "failure group" one was lower and the other higher than in the "remission group", and it was possible to calculate a ratio which could be used to indicate those patients who were unlikely to benefit from operation. This work emphasizes the fact that the hormonal status of the host is of great importance in determining response to endocrine treatment.

We have dealt with only some of the matters discussed in the report of Atkins *et alii*; for example, their observations on the post-operative hormone regime will interest anyone who has to deal with such patients. However, many will want to read this report in full, and enough has been said to indicate that this is an important contribution on a subject which is still in a stage of active evolution.

[1] *J. Amer. med. Ass.*, 1953, 151: 1388 (April 18).
[2] MED. J. AUST., 1954, 1: 249 (February 13).
[3] *Lancet*, 1957, 1: 489 (March 9).
[4] *Lancet*, 1960, 1: 1148 (May 28).
[5] MED. J. AUST., 1960, 1: 939 (June 11).
[6] *Lancet*, 1960, 1: 1154 (May 28).

MEDICAL SCHOOL FOR MONASH UNIVERSITY.

IN view of the importance of the development of a second medical school in Victoria, the following information, which has been supplied by the Vice-Chancellor of Monash University, will be of general interest.

The Interim Council of Monash University expects soon to receive authority to proceed to establish a medical school on the University site at Clayton, a suburb some twelve miles east-south-east of the City of Melbourne. The intention is to start the construction of buildings for the pre-clinical work as soon as possible, but, for the time being, clinical instruction will be carried out at two existing hospitals. In some years' time, when it is possible to construct a hospital on the Monash site, the clinical teaching will be centred there, but it is the hope and intention of the University that the two original hospitals will become permanent members of the Monash Medical School.

In view of the magnitude and complexity of the problems involved, the Interim Council intends that the Dean of Medicine shall occupy a full-time, permanent post of professorial status, and it has resolved to proceed at once to make an appointment to this position. The Dean will have the prime responsibility of advising the Council on the appointment of professors in the pre-clinical and clinical fields and on the broad policy to be adopted, including the general structure of the course and the arrangements for clinical teaching; he will also be responsible for giving general guidance to the architects on the design of the Medical School buildings.

Abstracts from Medical Literature.

SURGERY.

Intrathoracic Neurogenic Tumours.

O. SCHWEISGUH *et alii* (*Ann. Surg.*, July, 1959) report a study of 40 cases of intrathoracic neurogenic tumours in infants and children; 15 were neuroblastomas, seven ganglioneuroblastomas and 18 ganglioneuromas. The existence of clinical symptoms and intratumoral calcifications favoured a diagnosis of malignant disease. Thoracic cage deformities were related to tumour volume rather than growth characteristics. The authors discuss the therapy and they advise surgery alone for neuroblastomas in infants under two years of age and for all ganglioneuromas. They consider that post-operative X-ray therapy is indicated in the treatment of ganglioneuroblastomas and neuroblastomas in children over two years of age.

Smoking and Nutritional Status after Gastrectomy.

W. F. MITTY, L. M. ROUSSELOT AND G. J. DELANY (*Ann. Surg.*, July, 1959) report a five-year follow-up survey of 171 patients who had undergone partial gastrectomy, to determine the effects of smoking. These patients were followed for a minimum of two years. There were 115 smokers and 56 non-smokers. The conclusions reached were that no correlation existed between the amount of weight lost and whether or not a patient smoked; patients who smoked after their operation had no more significant digestive complaints than the non-smokers. However, it was found that more major late complications such as hæmorrhage, persistent vomiting and marginal ulcer occurred in the smokers.

Total Gastrectomy for High Gastric Carcinoma.

NILS STENSRUD (*Ann. Surg.*, July, 1959) presents the results of a five-year follow-up study of 160 patients treated by total gastrectomy for cancer of the stomach in the period from January, 1947, to February, 1952. Of these, 143 died during the immediate post-operative period, or within three years of operation; 17 lived for five years or more after operation. The author considers the prognosis for those who survived more than three years to be good. All surviving patients developed pernicious anæmia. Apart from anæmia and a moderate dyspepsia, the majority are living an active life with relatively minor discomforts.

Regenerative Hyperplasia of the Liver.

A. H. ISLAMI *et alii* (*Ann. Surg.*, July, 1959) present a study showing that in dogs, after 70% hepatectomy, the remaining liver assumes its normal size and weight within a period of two months. The chemical analysis of the liver substance in the regenerated lobe revealed a quantitative similarity of content for lipids and proteins. They interpret this finding as presumptive evidence that the regenerated liver tissue is probably identical in unit volume with the normal liver. They found that the nuclear counts of homogenized normal and regenerated liver tissue were essentially the same once hyperplasia was established.

Pulmonary Resection for Mineral Oil Granulomas.

L. D. GUIDRY *et alii* (*Ann. Surg.*, July, 1959) point out that through their remarkable mimicry of lesions of far more serious import, granulomatous tumours resulting from the aspiration of mineral oil have a significance unwarranted by their inherent disease potential. Asymptomatic aspiration of mineral oil occurs independently of defects of swallowing and in a higher percentage of normal individuals than is generally recognized. This mineral oil may be aspirated if the patient is taking it for constipation, or if spraying the nose for sinusitis. The authors report 11 cases in which pulmonary resection had been performed for mineral oil granulomas of the lung at the Mayo Clinic since 1947. These granulomas mimic a carcinoma, and the authors advocate exploratory thoracotomy for disease indistinguishable from carcinoma, regardless of whether or not mineral oil droplets can be detected in the sputum. They favour excision for symptomatic or extensive pulmonary involvement providing it can be accomplished without excessive sacrifice of normal lung tissue.

Ruptured Aneurysm of Aortic Sinus.

W. G. BIGELOW AND W. T. BARNES (*Ann. Surg.*, July, 1959) report two cases of ruptured aneurysm of the aortic sinus. Both were successfully treated surgically by open heart techniques, one with hypothermia and one with cardiac by-pass. In one right ventriculotomy was used to approach the aneurysm, and in the other right atriotomy, in each case accompanied by elective cardiac arrest. The opening of the aneurysm was closed with running silk sutures, which the authors consider was adequate without the necessity of buttressing the suture line with a patch of "Ivalon".

Hypothermia for Porta-caval Shunts.

R. H. CLAUSS *et alii* (*Ann. Surg.*, July, 1959) point out that cirrhosis of the liver is one of the 10 leading causes of death in the United States, and that it is fourth in the age group of 45 to 64 years. They cite clinical and laboratory experiences which support the thesis that hypothermia may be beneficial in porta-caval shunt operations upon patients with diffuse severe hepato-cellular disease. Five elective and five emergency porta-caval shunt operations under hypothermia are reported. All 10 patients survived operation.

Balanced Operations for Œsophageal Hernias.

J. K. BERMAN AND E. J. BERMAN (*A.M.A. Arch. Surg.*, June, 1959) point out that sliding œsophageal hiatus hernia is a malfunction of several of the derivatives of the foregut, and that in a significant number of patients there is an association of hiatus hernia with œsophagitis, duodenal or gastric ulcer, biliary tract disease and pancreatitis; the diaphragmatic defect may well be of ancillary importance. They maintain that operations which attempt to remedy the malfunction must be balanced so that there will be: (i) a restoration of the normal position of the œsophagus and stomach; (ii) a normal œsophago-gastric angle; (iii) a reduction in hyperacidity; (iv) a ready egress of gastric contents through a wide-open pylorus, thereby relieving intragastric pressure; (v) a correction of any associated disease of the foregut. The authors outline the procedures they have used to attain these objectives, and state that with this approach they have obtained uniformly good results in a series of 28 consecutive patients with sliding œsophageal hiatus hernia and œsophagitis. There was no operative mortality and no recurrence of herniation, and all patients except one, whose condition has improved, have been relieved of their symptoms for periods of up to eight years.

J. K. BERMAN AND E. D. HABEGGER (*A.M.A. Arch. Surg.*, October, 1959) discuss balanced operations for œsophagitis associated with hiatus hernia *en masse*. The technique of these procedures differs slightly in some cases from that of balanced operations for sliding hiatus hernia. The authors have obtained uniformly good results in 19 consecutive cases which have been followed for periods up to eight years.

Peptic Ulcer and Symptomatic Hiatal Hernia.

K. CRUZE, F. X. BYRON AND J. T. HILL (*Surgery*, October, 1959) emphasize the association of gastric and duodenal peptic ulceration with symptomatic hiatal hernia, and consider that this is more common than has been previously reported. They consider that, if peptic œsophagitis is seen, an intensive effort must be made to rule out the presence of a gastric or duodenal peptic ulcer, as peptic œsophagitis occurs nearly twice as frequently in patients with an associated peptic ulcer as in patients with symptomatic hiatal hernia alone. In their opinion, the transabdominal approach offers the most satisfactory technique by which a simultaneous repair of associated lesions can be effected. They consider that a combined ulcer and hernia repair should be seriously contemplated in any patient with a peptic ulcer, since this may save further major operations at a later date. The authors state that there is no evidence of cause and effect between these two lesions, since either may precede the other.

Meckel's Diverticulum.

T. N. JOHNS, J. R. WHEELER AND F. S. JOHNS (*Ann. Surg.*, August, 1959) present a study of 154 patients with a Meckel's diverticulum who were operated on between 1909 and 1958 at their hospital. Eleven patients with a Meckel's diverticulum were operated on between 1909 and 1937 and 143 between 1937 and 1958. During this latter period there were 22 cases in which disease involving a Meckel's diverticulum was

responsible for the patient's illness, whereas in the remaining 121 cases the diverticulum was an incidental finding in the course of operation for various other abdominal conditions. The authors state that the most frequent operation leading to the discovery of a Meckel's diverticulum is appendicectomy for suspected appendicitis, this being the pre-operative diagnosis in 100 cases in this series. Of the 22 cases with Meckel's diverticulum involved in a disease process, it was the cause of intestinal obstruction in six cases, diverticulitis was present in eight cases (in one with gangrene and perforation), in one the diverticulum was strangulated in an inguinal hernia and was gangrenous, in one it was found in a femoral hernia and was causing intestinal obstruction, in three it had caused intussusception, in two it had caused ulceration and hæmorrhage, and in one it was part of a persistent omphalomesenteric fistula. The authors think that in many instances the presence of an apparently uncomplicated Meckel's diverticulum can cause abdominal symptoms, but are doubtful as to the mechanism of this.

Anomaly of First Branchial Cleft.

D. GORE AND A. MASSON (*Ann. Surg.*, August, 1959) report a case of anomaly of the first branchial cleft. In a general discussion of the development of the neck they point out that the first branchial cleft becomes obliterated along a line extending from a point just below the mid-portion of the mandible and passes backwards parallel with the line of the mandible to end in the external auditory canal. Anomalies of development of the first branchial cleft are very rare, and in the majority of cases reported, the track of the first branchial cleft sinuses extends along the anterior border of the sternomastoid muscle to pass superficial to the posterior belly of the digastric muscle, and through the substance of the parotid gland superficial to the main trunk of the facial nerve, to end at the junction of the cartilaginous and bony parts of the external auditory canal, near the tympanic membrane. At this latter point it may end blindly or actually open into the external auditory canal. The authors point out that the presence of a persistent sinus high in the neck, associated with discharge from the ear in the absence of middle ear disease, should suggest the presence of an anomaly of the first branchial cleft. They state that only 12 cases of this anomaly have been previously recorded.

Acute Obstructive Cholangitis.

B. M. REYNOLDS AND E. L. DARGAN (*Ann. Surg.*, August, 1959) state that acute obstructive cholangitis presents a distinct clinical syndrome and requires early surgical decompression of the biliary tract. They point out that it is characterized by complete obstruction of the common bile duct with the accumulation of purulent material under pressure. The obstruction is most commonly due to calculi in the common bile duct, although strictures, neoplasms, pancreatitis and parasites may be the provoking agent. In the author's cases obstruction has been due only to calculi. In this syndrome the obstruction is functionally complete in all cases and leads to mental confusion and lethargy and profound shock. Thus the syndrome consists of the well-known clinical triad of chills and fever, jaundice and right upper quadrant abdominal pain or tenderness indicative of cholangitis. The addition of lethargy or mental confusion and shock to this triad represents acute obstructive cholangitis. The ideal management of this condition is early surgical decompression, and if this is achieved the patient, even though apparently often moribund at the commencement of operation, rapidly recovers. If operative intervention is delayed, death always ensues.

Fibrocystic Disease and Carcinoma of the Breast.

J. HODGE, J. SURVER AND G. G. APONTE (*A.M.A. Arch. Surg.*, October, 1959) review 876 cases of mammary carcinoma, and in this entire series the incidence of coexisting fibrocystic disease and cancer was only 3·1%. The authors consider that this figure does not support the thesis that fibrocystic disease of the breast is a precancerous lesion.

Hypophysectomy in the Treatment of Breast Cancer.

A. G. JESSIMAN, D. D. MATSON AND F. D. MOORE (*New Engl. J. Med.*, December 10, 1959) present a series in which 53 patients were subjected to surgical hypophysectomy for palliation of metastic mammary cancer. Forty-five patients were traced for periods from seven months to three years. Of these patients 60% had the course of the disease altered favourably. The authors found that the survival time of those obtaining an objective response was five times as long as those whose disease was not altered by the operation. The longest remission was 15 months and the longest survival was nearly three years. The authors consider that the most favourable patient for hypophysectomy is a woman 10 years post-menopausal, with disease involving the skin, lymph nodes, skeleton or lung, but not the brain, liver or viscera generally, who has a good cardiac, renal and pulmonary function, and who has shown evidence of a hormone-sensitive tumour by a favourable response to castration. The authors state that hypophysectomy should be the treatment of early metastatic spread of breast cancer rather than that of a diffuse or terminal disease.

Chemotherapy of Disseminated Carcinoma of the Breast.

J. C. WRIGHT *et alii* (*Ann. Surg.*, August, 1959) report a clinical investigation of the effects of chemotherapeutic agents on patients with advanced breast cancer. In this series chemotherapeutic agents were used alone in 67 incurable cases of cancer of the breast. In cases in which more than one drug was used in succession, these are counted as so many therapeutic trials. In this way 98 therapeutic trials are presented in relation to these 67 patients. No improvement occurred in patients treated with chlorambucil, the aminonucleoside of puromycin or actinomycin D. With the use of triethylene thiophosphoramide and "Amethopterin" temporary regression of the disease occurred in some cases. The authors conclude that for the palliation of patients with advanced disseminated breast carcinoma triethylene thiophosphoramide and "Amethopterin" may be added to the classical methods of radiation therapy and hormonal control therapy.

Pancreatic Biopsy with the Vim-Silverman Needle.

J. COTE, M. B. DOCKERTY AND J. T. PRIESTLEY (*A.M.A. Arch. Surg.*, October, 1959) discuss the results of biopsy of the pancreas, obtained by the Vim-Silverman needle from 83 patients, each of whom had a mass in the pancreas, but no obvious evidence as to the nature of the mass. All patients were followed up for three years after the operation. The histological diagnosis made on study of the rapid frozen section was confirmed in each instance when fixed sections were available. Of 53 patients who were known to have died of pancreatic malignant lesions, this lesion had been detected by biopsy in 68%. A similar study was made in 110 patients in whom a wedge type specimen was taken from the pancreas for biopsy. Fifty-six of these patients were known to have died of malignant disease of the pancreas, but the biopsy specimens had revealed the presence of a malignant lesion in only 46% of these. The authors therefore consider that the Vim-Silverman needle method is much more accurate than removal of a wedge biopsy. They point out that complications after removal of a pancreatic specimen by means of a Vim-Silverman needle seldom developed, and if they did, were inconsequential.

Post-Colectomy Regression of Rectal Polyps.

J. W. COLE AND W. D. HOLDEN (*A.M.A. Arch. Surg.*, September, 1959) discuss two male patients with diffuse polyposis of the colon and rectum who exhibited spontaneous regression of the rectal adenomas after total colectomy and ileoproctostomy. The adenomas in the retained part of the rectum nearest the anastomosis were the first to regress and those nearest the anal orifice the last. The authors found a diminution in the number of Feulgen-positive cytoplasmic inclusion bodies in the regressing polyps and a suggestion that nuclear deoxyribonucleic acid is decreased in amount. They did not think that inflammation and necrosis were the mechanisms responsible for the regression.

Carcinoma of the Tongue.

O. H. BEAHRS, K. D. DEVINE AND S. W. HENSON (*A.M.A. Arch. Surg.*, September, 1959) discuss 168 cases of cancer of the tongue seen at the Mayo Clinic between 1950 and 1953, and find that the five-year survival rate was 40%. They consider that the factors that influence prognosis are the location and size of the lesion, the grade of malignancy, and the presence or absence of metastatic lesions in the cervical lymph nodes. In this series the hospital mortality rate was 3·6%, which the authors consider can be reduced by the prophylactic use of anticoagulants, the free use of tracheotomy and other aids in post-operative care. They consider that early and adequate treatment by wide excision or hemiglossectomy, and the frequent use of radical dissection of the neck are necessary.

Brush Up Your Medicine.

THE NEPHROTIC SYNDROME.[1]

Ætiology and General Comments.

THE cause of idiopathic nephrosis is unknown.

It occurs predominantly in the second year of life and has been called "childhood nephrosis". The age incidence indicates the possibility of a single disease process, such as, perhaps, a general metabolic disorder with secondary involvement of the kidney.

It is commoner in boys than in girls, and is rare in adults.

Chronicity is characteristic.

Occasionally two cases have occurred in a single family.

The incidence is unknown. Some authorities have estimated 1 new case per 100,000 of the population *per annum*.

Predisposition to respiratory infections is common.

The nephrotic clinical pattern is rarely associated with a specific disease process, e.g., glomerulonephritis, particularly of the membranous or Ellis type II variety, amyloid disease, syphilis, intercapillary glomerular sclerosis (Kimmelstiel-Wilson's syndrome), tridione toxicity and disseminated lupus erythematosus.

The nephrotic syndrome also includes nephrotic nephritis. In this condition hæmaturia and other evidence of glomerular damage at the onset indicate a less hopeful prognosis. The clinical picture of the two conditions is occasionally very similar.

Basically, nephrosis is albuminuric hypoproteinæmia of sufficient severity to cause œdema.

The picture is: "pale puffy patient" and "pale puffy kidneys".

Pathology.

Macroscopic.—The kidneys are enlarged and yellowish. The external surfaces are smooth. The cortices are thickened and may show yellow lipoid deposits.

Microscopic.—Injury to the basement membrane of the glomerular capillaries and of Bowman's capsules, with subsequent thickening, is the typical pathological lesion in childhood nephrosis. The glomeruli become permeable to protein. Glomerular architecture is not distorted. Tubular changes are usually secondary to the glomerular lesions, but the precise role of the tubules is still in doubt.

Clinical Manifestations.

Œdema is the usual presenting symptom and often the sole complaint. Other symptoms are traceable to it. The periorbital area is first affected, and then the ankles. The œdema is typically recurrent, with partial or complete remissions. Diuresis is often spontaneous.

Oliguria is common, with a high specific gravity of the urine.

Albuminuria is present. The albumin-globulin ratio is between 10:1 and 20:1. A total of 10 to 15 mg. of protein, or more, may be excreted daily.

Proteinuria is the primary event in the genesis of hypoproteinæmia, which results in increased transudation from the plasma into the interstitial tissues.

Hypercholesterolæmia is usual.

Acidosis is not marked in the early stages.

The erythrocyte sedimentation rate is accelerated.

The basal metabolic rate is low.

The serum calcium and serum potassium levels may fall. The serum iron and serum copper levels are low. Some thyroxine may be lost.

The lipoprotein levels are raised.

Leucocytosis is common. Eosinophilia is fairly common.

Ascites, if present in the initial episode, has a more serious prognostic import. It is less ominous when it develops during a later exacerbation of the disease.

Microscopic hæmaturia can occur, but gross hæmaturia is uncommon.

Signs of glomerulonephritis, with hæmaturia, azotæmia and hypertension, eventually develop in some children who appear to have a typical lipoid nephrosis at the onset.

Persistence of the hæmaturia over long periods indicates progressive glomerulonephritis.

Pallor, failing appetite, lassitude and irritability may gradually develop, and in some cases malnutrition occurs.

Complications.

Complications include anæmia, diarrhœa, urinary infection, cellulitis of thighs or abdomen, strangulated umbilical hernia, fits, uræmia and coma. Abdominal pain and vomiting may simulate intussusception.

Prognosis.

The prognosis is relatively good. The severity of œdema may be a guide.

Drowsiness, azotæmia and hypertension are of serious significance.

Antibacterial therapy and prophylaxis have greatly reduced the death rate from infection, but they have had no effect in preventing the occasional case from developing into glomerulonephritis.

Corticosteroid therapy has further improved the prognosis.

The outlook in cases of nephrotic nephritis is very poor.

Treatment.

The following are the basic principles of treatment.

1. Prevention and control of acute infections are important. Prophylaxis with penicillin and sulphadiazine has been advocated as in rheumatic fever.

2. Nutrition should be improved and metabolic dysfunction corrected. Dietary protein should be adjusted to prevent negative nitrogen balance. So long as the urea clearance remains adequate, the patient should be given a diet of high protein content; but if the liver is already synthesizing albumin to its maximum capacity, obviously additional dietary protein can do no good. A high-calorie diet should be given to prevent endogenous tissue break-down.

3. Treatment should aim at increasing plasma volume, by reducing the stimulus of aldosterone secretion and the consequent sodium and water retention and potassium loss. Mercurial diuretics are contraindicated. Steroids are usually effective in inducing diuresis.

Steroid Therapy.

If infection is present, this should be treated first before steroid therapy is undertaken.

If hæmaturia is present, it is necessary to wait until it subsides before commencing treatment with corticosteroids.

The prednisolone dosage schedule (recommended by G. C. Arneil) is as follows, irrespective of the patient's age or size:

Days 1-10: 20 mg. 8-hourly (60 mg./day).
Days 11-20: 20 mg. 12-hourly (40 mg./day).
Days 20-: 10 mg. 12-hourly (20 mg./day).

The dosage of 20 mg. per day is then slowly reduced over a prolonged period, provided that the albuminuria continues to decrease.

Any sign of a gross increase in albuminuria is an indication to increase dosage, but it should be remembered that the concentration of protein in the urine will vary with the volume of urinary output.

If a favourable response is obtained from steroid therapy, proteinuria diminishes significantly, serum protein levels rise, hyperlipæmia decreases, and diuresis occurs. The onset of the diuresis may be delayed for no obvious reason.

Maintenance therapy may be necessary for many weeks or months in a dosage of 10-15 mg. of prednisolone daily. Intermittent stimulation of the adrenal glands with ACTH may be necessary if therapy is prolonged; it is especially necessary, daily, during the last week of corticosteroid treatment.

During hormone therapy the patient should receive a diet containing less than 2 mg. of sodium daily.

One should watch for side-effects, e.g., "moon-face", striæ and fæcal impaction. During rapid diuresis the plasma protein level may fall rapidly and convulsions may occur necessitating the administration of potassium chloride (1 gramme 6-hourly).

[1] No. 4 of a series of synopses prepared by Dr. Alex Johnson in collaboration with the Australian College of General Practitioners. Each synopsis has been submitted for approval to a leading member of the College, to a professor of pharmacology and to a specialist in the field concerned.

When steroid therapy is ineffective, chlorothiazide is of value in controlling the œdema, but it does not usually reduce the albuminuria. There is always the attendant danger of hypokalæmia.

In a number of cases, particularly in adults and when hypertension and hæmaturia are present in the early stages, treatment with steroids may fail. The initial dosage of chlorothiazide should be 500 mg. twice daily and this should be increased progressively by 500 mg. twice daily to as high as 2 grammes twice daily if no diuresis occurs.

The potassium level should be watched carefully when this more intensive treatment is being carried out.

ALEX JOHNSON.

British Medical Association.

NEW SOUTH WALES BRANCH: SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on April 21, 1960, at the Royal North Shore Hospital of Sydney. The meeting took the form of a number of clinical demonstrations by members of the honorary staff.

Novel Physiotherapy for Hemiplegia.

DR. DOUGLAS ANDERSON, with MISS V. M. PEARSON and MISS JOAN ANDERSON, demonstrated a novel form of physiotherapy, which had been used with what was described as outstanding success in the rehabilitation of a woman, aged 49 years, with right hemiplegia resulting from cerebral hæmorrhage. Dr. Anderson said that, from being a rather dreary and hopeless task, the recovery of hand and limb movements in the hemiplegic patient had become one of the most exciting and rewarding of physical treatments. Progress has stemmed from the notion of reeducation of movement instead of reeducation of muscles. The movements used were "basic patterns" of movement, most of which were in everyday use. It was found that the achievement of those could be enhanced by techniques of facilitation, known as proprioceptive neuromuscular facilitation (P.N.F.).

Exercises were performed in which patterns of movement were used in conjunction with the following sensory stimuli: (i) directional skin pressure—pressure of the physiotherapist's hands in the direction she wished the limb to move; (ii) stretching of muscles immediately before the movement was to take place; (iii) compression of or traction upon joints: (iv) the use of resistance; (v) the use of a stimulating tone of voice in commands; (vi) the use of "overflow" from normal muscles—moving the limbs of both sides simultaneously; (vii) brushing the skin on the extensor aspect of the forearm and hand—used in regaining finger and wrist control only.

Dr. Anderson emphasized that rehabilitation should begin at the earliest possible moment. As soon as the patient was able to cooperate, she had been taught how to turn from side to side in bed, to sit up and to change her position. Patterns of movement were taught on the sound limbs while the others were still in the flaccid stage, and standing and balancing had been practised very early. Distal reeducation was not attempted until proximal movements had been recovered. The new technique, which originated in California, had been in use in several hospitals in London for about a year, and was applicable to patients with joint diseases as well as to those with hemiplegia.

Varicella Pneumonia.

DR. J. ISBISTER showed a male patient, aged 41 years, who had developed varicella on February 13, 1960. Three days later his condition deteriorated, with weakness, dyspnœa and cough, and blood-stained sputum on one occasion. Physical examination showed him to be cyanosed and semicomatose, with a respiratory rate of 40 per minute and poor chest expansion; the percussion note was dull at the base of the right lung, and the breath sounds were vesicular except at the base of the right lung, where they were bronchial. Generalized coarse crepitations were present, most marked at the lung bases. His pulse rate was 124 per minute and his blood pressure 130/70 mm. of mercury. The skin showed generalized varicella rash, and his temperature was 101·2° F. One hour after his admission to hospital his condition had deteriorated, Cheyne-Stokes respiration and decreased alertness being present. However, oxygen given intranasally produced improvement, and he was given (i) erythromycin, (ii) penicillin, (iii) "Solu Cortef", 100 mg. *statim* and 100 mg. in six hours, and then cortisone orally, 100 mg., and 50 mg. every six hours. A strict fluid balance record was kept, and barrier nursing was carried out. The hæmoglobin value was 17·4 grammes per 100 ml.; the leucocytes numbered 8700 per cubic millimetre, 44% being neutrophils, 14% lymphocytes, 30% band forms, 9% monocytes and 3% Türk cells.

His condition continued unchanged for several hours, but by eight hours after his admission his colour and alertness had improved, and his temperature had fallen to 99·2° F. His progress to recovery was then very rapid, and by February 20 few chest signs were present. Antibiotics were given because of uncertainty as to whether the condition was primary varicella pneumonia or a secondary infection. X-ray examinations of the chest, which on February 18 had shown bronchopneumonic changes throughout both lungs (changes most typical of varicella pneumonia), showed considerable clearing in both lungs by February 23, and by February 25 the changes in the film were very few. He was discharged from hospital on February 25, to complete his convalescence at home, being given no further treatment.

Goodpasture's Syndrome.

Dr. Isbister then showed a male patient, aged 49 years, who in 1958 had had an attack of bronchitis and coughed up bright red blood. He had had no further attacks until June, 1959, when he had hæmoptysis for two weeks accompanying a mild bronchitis. He then spat up one teaspoonful of blood 10 to 12 times per day. He was at that time admitted to the Thoracic Unit at Royal North Shore Hospital, where investigations, including a bronchoscopy, a laryngoscopy and a barium-meal X-ray examination, revealed no abnormality. The blood urea content was normal. After his discharge from hospital the patient had recurrent hæmoptysis; he complained of weakness, dyspnœa, cramps in the leg, nausea, dullness of vision in the right eye and huskiness of his voice. He had no cough, no chest pain, no jaundice and no bruising.

On physical examination of the patient, his blood pressure was found to be 210/120 mm. of mercury and his pulse rate 108 per minute. Presystolic gallop rhythm was heard. No other abnormalities were found. Blood examination showed that his hæmoglobin value was 8·1 grammes per 100 ml.; the leucocytes numbered 9100 per cubic millimetre and had a normal distribution. His blood urea content was 135 mg. per 100 ml. He was given a transfusion of two bottles of packed cells, and his hæmoglobin value rose to 12·2 grammes per 100 ml.

On September 25, 1959, a bronchoscopic and œsophagoscopic examination was made. Blood was seen in the right and left main bronchi, and bleeding points were found in the right middle bronchus and the left middle bronchus. Œsophagoscopy revealed no abnormality. A bronchial biopsy was taken.

On October 3 he became drowsy and anorexic and started to vomit. These symptoms persisted, and it was thought that the patient was suffering from renal failure. His condition gradually deteriorated. On October 13 he began to have convulsions. His condition failed to improve, and on November 12 he died.

Post-mortem examination showed, in the kidneys, changes indicating an acute terminal exacerbation of chronic glomerular nephritis. There were several completely fibrosed glomeruli, and many had increased lobulation. Many of the tubules contained blood. There was evidence of periarteritis nodosa. The bronchi contained copious, deeply blood-stained frothy sputum. Microscopic examination of sections showed hæmorrhagic pneumonitis. The over-all findings confirmed the clinical picture of Goodpasture's syndrome.

Hodgkin's Disease.

DR. D. W. PIPER and DR. MIRJAM STIEL showed two patients to illustrate unusual features of Hodgkin's disease.

The first patient was a man, aged 53 years, who presented with fever and a large gastric ulcer, the latter later perforating. From 1953 to 1955 he had several episodes of epigastric pain relieved by antacids, each episode lasting several weeks. In October, 1955, a barium-meal X-ray examination revealed a gastric ulcer on the middle third of the lesser curvature. The patient was treated on an ulcer régime with relief of symptoms. In December, 1958, he had a recurring episode of severe epigastric pain, different in character from the previous attack and no longer relieved by antacids. A barium-meal X-ray examination now showed

a greater curve ulcer. He was found to have a persistently high temperature, and was referred to the Royal North Shore Hospital. Physical examination of the patient on his admission revealed no abnormality except slight epigastric tenderness. Investigations showed a normal blood count, normal X-ray findings in the chest and a slightly elevated blood urea level. A barium-meal X-ray examination showed a large greater curve ulcer, possibly malignant. Scalene node biopsy revealed no abnormality. While the patient was in hospital, fever and epigastric pain persisted, and on February 20, 1960, the ulcer perforated. A partial gastrectomy was performed, and subsequent microscopic examination of the stomach revealed the presence of Hodgkin's disease. A fat-balance study performed later showed that the patient had steatorrhœa, 30 grammes of fat being excreted on an intake of 100 grammes. The patient was treated with nitrogen mustard and deep X-ray therapy to the stomach area.

The second patient was a man, aged 56 years, who presented himself with a diffuse pulmonary infiltrate and skin lesions. In 1953, a routine chest X-ray examination had revealed enlarged hilar lymph nodes. He was diagnosed and treated as suffering from tuberculosis, with apparent radiological improvement. In 1955, a round opaque area in the right upper zone was found on follow-up X-ray examination; the lesion was removed, but the pathological findings were not known. From 1956 to 1957 the patient experienced transient enlargement of axillary and inguinal lymph nodes, and developed a right pleural effusion which was aspirated and did not recur. In 1958, the patient developed a swelling near the angle of the jaw on the right side. It was removed, and was found to be a mixed parotid tumour. At that time the patient was found to have a raised leucocyte count, with immature leucocytes and nucleated red cells. Progress blood counts over the next two years gave similar results. In February, 1960, the patient presented to the Anti-Tuberculosis Association with a six weeks' history of fever and cough and sputum and hæmoptysis for several days. Chest X-ray examination revealed diffuse infiltration of both lung fields. The patient was admitted to Royal North Shore Hospital for diagnosis and treatment. On examination, he was found to have an enlarged liver and spleen. Skin lesions were present on both arms and legs. No enlarged lymph nodes were palpable. An X-ray examination of his chest revealed a diffuse opaque area extending outward from the hilar region, and throughout the greater part of both lungs there was fine irregular mottling. The leucocytes numbered 23,000 per cubic millimetre, 83% being neutrophils, 3% eosinophils, 4% basophils, 2% neutrophil myelocytes and 2% myeloblasts. The response to the Mantoux test was positive, but culture of the sputum failed to yield a growth of acid-fast bacilli. Liver function tests produced normal results. Marrow biopsy revealed the presence of Hodgkin's disease. Biopsy of the skin lesions showed non-specific chronic inflammation. The patient was treated with nitrogen mustard, a total dose of 40 mg. being given in divided doses.

Torsion of an Undescended Testis.

MR. E. GOULSTON showed a male infant, aged seven months, who had been admitted to hospital on November 17, 1959, because of a swelling in the right groin, which the parents had noticed for several hours, but which might have been present for much longer, as the baby had been crying and irritable for the previous 36 hours. He was known to have had an inguinal hernia on both sides. On the baby's admission to hospital, no testes were found in the scrotum, and a tense, tender swelling was palpable in the right groin. An urgent operation was done, and orchidectomy was performed for torsion of a gangrenous ectopic testis on the left side. Convalescence was uneventful, and as the remaining testis was undescended, it was decided to attempt an orchidopexy on the right side, despite the patient's age, rather than risk a similar episode. A second operation was therefore performed on November 26, and an ectopic testis with a hernial sac was successfully dealt with.

Mr. Goulston said that, in bilateral undescended testis, if a torsion or incarceration of a hernia occurred, early operation was essential whatever the age of the child. If that testis was damaged or infarcted, then an early second operation should follow on the good side.

Common Duct Calculus without Jaundice.

MR. T. F. ROSE's first case illustrated the value of the intravenous injection of "Biligrafin" in the detection of common duct calculi not causing jaundice. The patient, aged 50 years, had suffered from a severe attack of acute gangrenous cholecystitis due to the impaction of a calculus in the cystic duct. He was also slightly jaundiced, and at operation many small calculi were found in the common bile duct. The gall-bladder was removed and the calculi were removed from the common bile duct, which was sutured, and a drain was placed down to it. The patient remained well for one year, but he then developed attacks of severe epigastric pain radiating to the right hypochondrium. The attacks occurred at any time and were not associated with either vomiting or jaundice. Physical examination revealed no significant abnormality. There was no jaundice and no liver enlargement. Radiography with "Biligrafin" revealed a constant filling defect in the common bile duct: at operation it was verified as being a small gall-stone, and was easily removed. The sphincter of Oddi was patent.

Large Pelvic Chondroma.

Mr. Rose's next patient was a man, aged 40 years, who was known to have had a pelvic mass on the right side for 12 years. It was becoming gradually larger, until it almost filled the pelvic cavity. It had also grown downwards into the inner aspect of the thigh, so that the patient found difficulty in walking owing to its mechanical interference with the femur. Examination of the patient disclosed a large hard mass occupying the right side of the pelvis and continuous with the mass in the right thigh. There was restricted movement of the right hip joint. Rectal examination showed that the rectum was pushed over to the left. A radiographic examination showed an enormous chondroma replacing the right side of the pelvis, and even forming the acetabulum. Intravenous pyelography revealed a right hydronephrosis and hydroureter, though with good renal function. Femoral angiography showed that the blood supply of the tumour was from the internal iliac vessels. At operation, a great deal of the abdominal mass was removed, and later the thigh extension. Hæmorrhage was copious, even though the internal iliac artery was ligated. The tumour was multiloculated, bony and cartilaginous, as if normal bone was expanded. Much of it was jelly-like material. The pathologist diagnosed chondroma, with no evidence of malignant change. At the time of the meeting, the patient's condition was improved.

Liver Angioma Causing Hæmobilia.

The third patient shown by Mr. Rose was a woman, aged 50 years, who had been known for four years to have an abdominal mass which caused aching pain intermittently. Examination of the patient disclosed a large, smooth, rounded mass projecting below the right costal margin. It was not tender, and it felt firm. A barium-meal X-ray examination revealed no abnormality. A Graham's test revealed a well-functioning gall-bladder of normal shape behind and to the left of the mass. An intravenous pyelogram revealed normal kidneys, the right being behind the mass, which was calcified in a speckled manner. Operation was advised, but the patient was against it until she had a sudden melæna with faintness and weakness following an exacerbation of right-sided upper abdominal pain. At operation a week later, with a blood transfusion, a large pedunculated venous hæmangioma, 3 in. by 2 in., in the anterior margin of the liver was excised from the liver with little difficulty. It was lateral to the gall-bladder. The mass was spongy and felt gritty owing to calcification. There were no large feeding vessels. No blood was seen in the intrahepatic bile passages or gall-bladder, which appeared normal. The rest of the alimentary canal was normal. The pathological finding was that of a simple angioma with areas of calcification. Mr. Rose said that it seemed that some part of the angioma must have communicated with the intrahepatic biliary system and caused hæmobilia leading to a severe melæna. The patient had remained well in the ensuing 12 months.

Adult Megacolon.

Mr. Rose's fourth patient was a man, aged 68 years, who had been well until two years previously; since then he had suffered from recurrent attacks of precipitancy of defæcation with large fluid motions, and some generalized colicky pains prior to the passage of the fæces. Before each attack he noticed distension of the abdomen, especially on the left side. Examination of the patient during an attack revealed enormous abdominal distension, especially on the left side. Rectal examination revealed no abnormality. X-ray examination with a barium enema revealed a huge megacolon localized to the upper descending colon and the left side of the transverse colon. Saline enemas relieved the condition. After adequate preparation, laparotomy was performed, the dilated portion was excised through bowel of normal calibre at each end, and end-to-end anastomosis was performed. Convalescence was uneventful, and all was still well four years later. Mr. Rose said that the specimen was enormously

dilated; it was 35 cm. long, and had a circumference of 23 cm. Microscopic examination of sections from each end and also from the normal-sized adjoining bowel showed normal Auerbach's and Wiessner's plexuses.

Mr. Rose's last patient was a woman, aged 63 years, who gave the history that four years previously her local doctor had performed a laparotomy and removed an ovarian cyst. He had made a special note at the time that the patient had no fixation of her colon at all, the whole colon from and including the caecum to the rectum being on a long almost mid-line mesentery and situated to the left of the small bowel. However, at that time the colon was normal in size and calibre. She remained well until nine days prior to her admission to hospital, when she commenced to have recurrent attacks of colicky right-sided abdominal pain with distension and constipation. These were relieved by the passage of wind and fluid motions, but kept recurring and becoming worse. Examination of the patient disclosed mild abdominal distension, especially on the right side. Pelvic and rectal examination disclosed a cystic mass in the pelvis, which turned out later to be caecum. X-ray facilities were not available at that time. The patient was vomiting and dehydrated, and after gastric suction and intravenous therapy had commenced, laparotomy disclosed a chronic type of partial volvulus of all the colon from the ileum to the pelvi-rectal junction. The bowel was on a long mesentery attached to the mid-line. The volvulus was untwisted. The terminal portion of the ileum was divided, the distal end was closed and the proximal portion was inserted into the rectum. Fourteen days later the blind loop was excised. The specimen was grossly dilated and thinned out, and full of liquid fæces. Convalescence was reasonable, except for diarrhœa for some weeks.

Ruptured Abdominal Aortic Aneurysm Treated Surgically.

MR. G. D. TRACY showed two patients who had undergone surgical treatment of a ruptured abdominal aortic aneurysm.

The first patient, a man, aged 73 years, had been admitted to hospital on December 14, 1959, with a history of lower back pain of 12 months' duration. In the last two months the pain had become increasingly severe, radiating into the abdomen. The patient had a past history of myocardial infarction in 1957, and had recently experienced difficulty with micturition. Examination of the patient revealed a pulsating abdominal mass with marked tenderness. The pulse rate was 100 per minute and regular; the blood pressure was 190/105 mm. of mercury. Rectal examination showed prostatic enlargement. Included among the investigations was a radiological examination of the chest, which showed no abnormality, and an electrocardiogram showing "possible ischæmic changes with ventricular ectopics". The blood urea content was 55 mg. per 100 ml. A diagnosis of abdominal aortic aneurysm was made, and the patient was submitted to operation on December 23. Sudden increase in pain had been noted on the day of operation, and laparotomy disclosed a large aneurysm of the terminal portion of the aorta, 10 cm. in diameter, which had burst into the retroperitoneal tissues; there was free blood in the peritoneal cavity. The aorta was cleared above the aneurysm and both common iliac arteries below. After intraaortic injection of 2 mg. of heparin, arterial clamps were applied and the aneurysm was excised, that part of the aneurysm wall being left which was adherent to the inferior vena cava. A bifurcated "Teflon" tube was used to replace the aorta, and sutured to the aorta with continuous 3/0 arterial silk sutures and to each common iliac artery with 4/0 arterial silk sutures. The clamps were released 110 minutes after application. The operation time was four hours, and the blood loss measured by aspiration and sponge weighing was 1400 ml. Five units of whole blood were given during and after the operation. After closure of the abdominal wound, no pulse could be felt in the right femoral artery. A groin incision was made to expose that artery, which was incised, but no intraluminal clot or obstruction could be found. Mr. Tracy said that the patient's convalescence was uneventful, apart from some prostatic obstruction which required an indwelling catheter. When the patient became ambulant, the catheter was removed with no further difficulty, and he was discharged from hospital on January 16, 1960.

Mr. Tracy's second patient was a woman, aged 90 years, who had been admitted to hospital on January 2, 1960, with a history of severe central abdominal pain spreading into the back, of 20 hours' duration. Before the onset of the pain she had been active and well, and had not sought medical attention for the preceding 15 years. Examination of the patient revealed a large pulsating abdominal mass about 7 cm. in diameter. The pulse rate was irregular, 72 per minute, and the blood pressure was 150/80 mm. of mercury. Significant investigations included a chest X-ray examination, showing moderate emphysema and cardiac enlargement, and an electrocardiogram, which showed ischæmic changes and supraventricular ectopic beats. A provisional diagnosis of leaking abdominal aneurysm was made, and the patient was submitted to laparotomy three hours after her admission to hospital. Operation revealed a large aneurysm involving the terminal portion of the aorta, which had ruptured into the retroperitoneal cavity. The aorta above the aneurysm, and both common iliac arteries below it, were dissected free and occluded with arterial clamps after the intraaortic injection of 2 mg. of heparin. The aneurysm was then excised and replaced with a woven "Teflon" tube, which was sutured to the aortic ends with 3/0 arterial silk sutures. The clamps were released to restore the circulation to the lower limbs one hour after occlusion. The operation lasted three hours, and the blood loss estimated by aspirate and sponge weighing was 1000 ml. Three units of whole blood were given during the operation. After the operation the patient developed anuric renal failure, the blood urea level reaching 335 mg. per 100 ml. by the eighth day after operation. A polyvinyl catheter was inserted through the saphenous vein into the inferior vena cava to maintain an infusion regulated to provide 400 ml. in excess of each 24 hour output. Diuresis began on the fifth post-operative day, and gradual improvement in the patient's condition allowed oral feeding on January 19, the catheter being removed on the following day. Improvement was maintained until the patient's discharge from hospital on February 6.

Chemotherapy in the Treatment of Malignant Disease.

MR. I. MONK and MR. T. S. REEVE showed two patients to illustrate the use of chemotherapy in malignant disease.

The first, a man, aged 42 years, had been admitted to hospital for investigation of pain and radiological abnormality in the right side of his chest of three months' duration. The pain was pleuritic in nature, commencing in the mid-zone and radiating to the shoulder and back, and was increasing in severity; dyspnœa on mild exertion had been noticed since the onset of pain. X-ray examination revealed a diffuse process involving all areas of the right lung, with fluid accumulation at the base of that lung. On examination of the patient, limited chest movement, diminished percussion note and diminished breath sounds on the right side were noted. Pleural biopsy was performed, pleural seeding was observed and the histological findings were those of oat-cell carcinoma. In view of the grave prognosis and the comparative youth of the patient, radical chemotherapy was administered. Under general anæsthesia 85 ml. of bone marrow were aspirated from the sternum and both iliac crests, 120 mg. (1·5 mg. per kilogram) of nitrogen mustard were then given intravenously over a period of 40 minutes, and the bone marrow was replaced intravenously. Two units of gamma globulin were administered. After operation, the patient suffered severe vomiting for 24 hours, and also noted perceptive deafness. Over the ensuing two weeks his leucocyte count fell from 11,900 to 450 per cubic millimetre, and the number of platelets from 779,000 to 61,000 per cubic millimetre. However, at that stage the replaced marrow began to take over, and at the time of his discharge from hospital five weeks after therapy the leucocytes numbered 8900 per cubic millimetre and the platelets 685,000 per cubic millimetre. The initial hæmoglobin value of 14·2 grammes per 100 ml. fell to 11·7 grammes per 100 ml., but was 14·8 grammes per 100 ml. at the time of his discharge. A unit of fresh blood was administered when all former elements of the peripheral blood reached their lowest level. At the time of his discharge, the patient's hearing had improved considerably, the chest pain was relieved, and there was considerable clearing of the X-ray changes in his chest. He was discharged from hospital on oral maintenance therapy with "Endoxan" (cyclophosphamide) in a dosage of 100 mg. per day. It was stated that the X-ray changes in his chest had shown some further clearing, and clinical improvement had been maintained.

The second patient shown by Mr. Monk and Mr. Reeve was a man, aged 61 years, who had been well until Christmas, 1959, when he developed a dry cough. An X-ray film showed a shadow in the left side of his chest. A bronchoscopic examination was performed, and the patient was told that he had a growth which was inoperable. He came to Sydney for a further opinion; during the previous month he had become anæmic and lost weight. During the three or four days prior to his admission to hospital in February, 1960, he had noticed that his urine was darker and his stools were pale. On examination, the patient was seen to have jaundiced skin and conjunctivæ. There was a hard fixed lymph node overlying the clavicular head of the

right sterno-mastoid. Expansion was diminished over the left side of the chest, resonance was diminished over the left lower zone, and air entry was diminished over the whole of the left lung. An X-ray film of the chest revealed a large mass with irregular margins extending posteriorly from the left hilar region: the left hemidiaphragm was much elevated, the appearance suggesting phrenic nerve paralysis due to invasion of the nerve by tumour. The liver was palpable 3 in. below the costal margin. There were no other abnormal findings. The serum bilirubin level was 5·6 mg. per 100 ml., and the alkaline phosphatase content 18 King-Armstrong units. A decision was made to use chemotherapy, and "Endonan" (cyclophosphamide) in a dosage of 75 mg. per kilogram was administered intravenously. A week after treatment the leucocyte count was 350 cells per cubic millimetre, and the platelet count was normal; the leucocyte count remained at a depressed level for four days and then steadily rose to normal. During the week after his admission to hospital the patient's appetite and sense of well-being improved, the jaundice disappeared, as did the lymph node in his neck, and the liver decreased in size. The serum bilirubin level fell to 0·9 mg. per ml., and the alkaline phosphatase level fell to 7 King-Armstrong units on the ninth day after therapy and remained normal. An X-ray film of the chest at the time of his discharge from hospital, three weeks after therapy, showed a marked decrease in the size of the left hilar mass. It was stated that the patient was being maintained on 100 mg. of "Endoxan" per day taken orally, and 200 mg. by intravenous injection once a week. He had returned to full activity and continued to feel well. He had suffered from hair falling.

The comment was made that the two patients had shown an immediate response to chemotherapeutic agents. Those agents were more effectve in rapidly-growing anaplastic tumours; but they did not have a beneficial effect in all cases. Other tumours besides carcinoma of the lung responded to treatment; but it was not always so easy to gauge response as it was by following the results on serial X-ray films. There was little doubt that cytotoxic and cytostatic agents were available which could produce temporary improvement in a number of patients with malignant disease; more particularly they could assist in making such patients more comfortable, and that was of considerable importance in the management of patients with malignant disease.

Atrial Septal Defect.

DR. D. STUCKEY and DR. R. G. EPPS showed a boy, aged seven and a half years, with an atrial septal defect. The boy had first attended the Cardiac Investigation Clinic for investigation of a cardiac murmur detected at a routine medical examination at the age of two and a half years. He had never made any complaint of limitation of exercise tolerance or any other symptoms. He had been examined yearly in the Cardiac Clinic. On examination of the child, there was no cyanosis or clubbing. He was of small build, and had abnormal chest development. The blood pressure, jugular venous pressure and pulse were all normal. Palpation of the precordium revealed both left and right ventricular activity, and it was thought that the right ventricular impulse was dominant. There was a palpable pulmonary artery impulse and the pulmonary second sound was palpable. There was a systolic thrill of Grade IV intensity, maximal in the fourth intercostal space in the mid-line and in the fourth left intercostal space close to the sternum. A systolic murmur of Grade IV intensity was audible in the same situations. A mid-diastolic murmur of Grade I-II intensity was also audible, being maximal in the fourth left intercostal space. The pulmonary second sound was split and fixed. An electrocardiogram revealed broad *P* waves and *RSR* complex in the anterior chest leads, and a prolonged *P-R* interval. X-ray examination of the chest revealed cardiac enlargement with prominent pulmonary artery and increased pulmonary plethora. Cardiac catheterization was carried out on March 31, 1959, and revealed a large shunt at the auricular level, indicating the presence of an atrial septal defect. It was the opinion at the Cardiac Clinic, in view of all the data, that the boy probably had an ostium primum defect. He was attending the Clinic for follow-up examination.

The second patient shown by Dr. Stuckey and Dr. Epps was a boy, aged 16 years, who had been referred to the Cardiac Investigation Clinic because of the discovery of a cardiac murmur at routine physical examination. He was asymptomatic, and had a normal exercise tolerance. There was no relevant past or family history. He was not cyanosed, there was no finger clubbing, and his general build was normal. His pulse and blood pressure were normal. The jugular venous pulse showed an accentuated *A* wave. The cardiac impulse revealed considerable right ventricular lift at the left sternal edge, and there was palpable pulmonary artery pulsation. No thrills were palpable. A Grade II systolic murmur was audible in the pulmonary area and down the left sternal edge. A soft early diastolic murmur was also audible in the third left intercostal space. The pulmonary second sound was widely split and fixed. An electrocardiogram showed a pattern consistent with right ventricular dominance, and there was an *RSR* pattern in leads V_3 to V_6. An X-ray examination of the chest revealed cardiac enlargement, and pulmonary plethora was obvious. Cardiac catheterization was carried out on October 21, 1958, and proved the presence of an atrial septal defect, which had been diagnosed clinically. There was a shunt through the defect of 5·5 litres per minute. On March 23, 1959, a simple secundum-type atrial septal defect was repaired under hypothermia through a sternum-splitting incision. Convalescence was uneventful. The patient had been last seen in the Chest Clinic on January 12, 1960. He was symptom-free. There was still wide splitting of the second heart sound, but no other signs of atrial septal defect. An X-ray examination showed that the heart had become smaller, but was still slightly enlarged. An electrocardiogram still revealed right bundle branch block and some evidence of right ventricular hypertrophy. However, it seemed that these signs were regressing slowly.

Hydatid Disease of Lung.

DR. G. MCMANIS showed a girl, aged 16 years, with hydatid disease of the lung. She lived on a sheep station near Grenfell, and had been admitted to hospital with a history of cough of ten months' duration and sputum with hæmoptysis of three months' duration, which followed an attack of right basal pneumonia in November, 1959. Hæmoptysis, sputum and coughing were present on her admission. On examination, the patient was seen to be a young girl of the stated age, in good health. Vesicular breath sounds were present, softer on the left than on the right, and vocal resonance was decreased on the left. Her pulse rate was 64 per minute; her blood pressure was 120/70 mm. of mercury. A provisional diagnosis of unresolved pneumonia with a secondary diagnosis of hydatid disease was made. The patient was treated with penicillin (500,000 units every eight hours), breathing exercises and tipping. A Casoni test indicated hydatid disease, but it was not known whether the patient had previously had one. X-ray examination on her admission showed an opaque area at the base of the left lung, which was circumscribed, and which from the lateral films appeared to lie in the lower lobe posteriorly. Subsequent X-ray films indicated a clearing of the surrounding mottling and an increase in the hardness of the round lesion in the lower left zone. Penicillin, breathing exercises and tipping were continued, but no further improvement occurred. Bronchoscopy was performed, and no abnormality was found. Subsequent thoracotomy revealed a hydatid cyst, which was removed, with a sub-segmental resection of the posterior segment of the lower lobe. Convalescence was uneventful. The pathological report on the excised tissue was as follows:

> A. This is a piece of hydatid ectocyst. B. There are areas of collapse and chronic inflammation in the lung. There is a thick fibrous wall in one part, on the inside of which are acute and chronic inflammatory cells.

Œsophageal Cyst.

Dr. McManis' second patient was a healthy girl, aged 14 years, who had presented herself with one episode of hæmoptysis eight weeks before her admission to hospital. No other symptoms were reported. X-ray examination indicated an opaque area in the right upper zone. There were no abnormal physical findings. A series of tests were carried out in hospital, and X-ray films indicated a round shadow in the right upper zone, while in the lateral film a dense shadow beyond the round opaque area was observed. Tomography showed some breakdown in the lesion, and the bronchoscopic findings were normal. As a positive diagnosis had not been reached, thoracotomy was performed, and a foregut cyst was removed, with the resection of the posterior segment of the upper lobe of the right lung. After operation her recovery was uncomplicated and rapid. Histological examination of the specimen showed it to consist of an œsophageal cyst with œsophageal mucus glands, striated muscle and smooth muscle.

Neurosurgery in Epilepsy.

DR. R. G. RUSHWORTH gave a demonstration illustrating the role of neurosurgery in epilepsy. It was stressed that epilepsy was a symptom which had a widely varied ætiology.

and that surgery was indicated in only a small percentage of cases, as in most cases the seizures could be controlled with anticonvulsants. All patients for whom operation was contemplated required a most intensive work-up, with particular emphasis on the history and neurological examination, and expert interpretation of the electroencephalograms. Special techniques, such as sphenoidal lead recording, were employed to detect epileptic discharges in inaccessible parts of the brain, and activation with "Pentothal" or "Megimide" was used to reveal areas of brain damage and latent foci. An attempt to remove the area of brain containing the epileptogenic area was indicated if it could be accurately located and was situated in an area where removal would not produce serious neurological deficit, and if the patient's seizures were poorly controlled by medication. The results of temporal lobectomy were gratifying if the patients were carefully selected, and the neurological deficit resulting was slight.

Corticosteroid Therapy in Rheumatoid Arthritis.

DR. P. J. BENJAMIN, DR. R. G. ROBINSON, DR. J. B. DICK-SMITH, DR. R. H. MACOURT and DR. R. SWINBURN presented five cases illustrating undesirable side effects of corticosteroid therapy manifested by patients undergoing a carefully controlled trial. The patients were all suffering from rheumatoid arthritis which had not responded to all the usual measures included in general management of the disease. Once a decision was made to use corticosteroids, each case was carefully assessed for inclusion in the trial. The corticosteroids in use were prednisolone, methyl prednisolone, triamcinolone and dexamethasone. Each patient was established on a dose considered to be equivalent in effect to 15 mg. of prednisolone per day, and carefully observed every two weeks. The side-effects were therefore considered to be those which might be observed when corticosteroids were used carefully in the average case of rheumatoid arthritis. The cases were presented for that purpose, and not to demonstrate the more florid changes which could easily be precipitated by injudicious treatment of unsuitably selected sufferers.

Bladder-Neck Obstruction.

MR. ROBERT D. SMITH first showed a girl, aged eight years, who had suffered from dribbling incontinence of urine by day and nocturnal enuresis all her life. She had had tuberculous meningitis as a baby. Examination of the child showed her to have a distended bladder and infected urine; the residual urine amounted to 12 oz. The blood urea content was 60 mg. per 100 ml. There was gross bladder trabeculation with pseudo-diverticula. Intravenous pyelography showed bilateral hydronephrosis and poor dye concentration. The diagnosis was thought to be (i) possible neurogenic bladder, secondary to tuberculous meningitis and (ii) bladder-neck obstruction. In October, 1959, a plastic operation on the bladder neck was performed. This was done in an effort to improve the child's condition and to avoid a urinary diversion operation. It was thought at the time, however, that the bladder condition was more typical of neurogenic origin. After operation the child had diurnal continence at all times, although she still wet the bed at night. She had no residual urine, and the urine was sterile with the administration of 50 mg. of "Furadantin" twice a day. An intravenous pyelogram in April, 1960, showed prompt bilateral renal excretion at five minutes, with very slight hydronephrosis on the right side and almost normal calyceal and pelvic outline on the left.

Idiopathic Megaureter.

Mr. Smith's second patient was a girl, aged four years, who had suffered from recurrent left-sided abdominal pain and urinary infection resistant to chemotherapy. Tenderness in the left loin was present, and the urine was infected. The cystoscopic findings were normal, apart from slight cystitis. The ureteric orifices were normal, and there was no ureteric blockage. Intravenous pyelography revealed left hydronephrosis and hydroureter. A diagnosis of idiopathic megaureter was made. In July, 1958, left uretero-neocystostomy was performed. Intravenous pyelography in January, 1959, revealed no abnormality. Mr. Smith said that since operation the child had been asymptomatic, and the urine was sterile three months after operation.

Mr. Smith also showed a boy, aged nine years, who had suffered from increasing difficulty in micturition for 12 months with increased frequency of micturition. He had a distended bladder and a poor urinary stream, and the residual urine amounted to more than 10 oz. The urine was infected. Cystoscopic examination revealed a trabeculated bladder and marked narrowing of bladder neck, with normal ureteric orifices. Intravenous pyelography revealed hydronephrosis and hydroureter. In September, 1958, a plastic operation on the bladder neck was undertaken. After operation the patient had a good urinary stream, no residual urine and complete urinary control, and within two months of surgery the urine was sterile and had remained so without chemotherapy. In April, 1959, intravenous pyelography showed a satisfactory state of affairs, with no hydronephrosis and no hydroureter.

Mr. Smith finally showed a boy, aged six years, who had had a very poor urinary stream since he was a baby. At the age of six years he could pass urine only sitting down and with great difficulty. He had a distended bladder and a trickling urinary stream, and the residual urine amounted to 6 or 7 oz. Slight urinary infection was present. Cystoscopic examination revealed gross trabeculation and a narrowed bladder neck. The ureteric orifices were normal. Intravenous pyelography revealed gross bladder trabeculation and normal upper urinary passages. A cystogram showed gross trabeculation. In September, 1958, a plastic procedure on the bladder neck was undertaken. After operation the child had a good urinary stream, complete urinary control and no residual urine. The urine was sterile within two to three months of operation, and had remained so. In April, 1959, a normal cystogram was obtained.

Out of the Past.

THE PRINCE ALFRED HOSPITAL, SYDNEY.[1]

[From the *Australasian Medical Gazette*, July, 1900.]

A CIRCULAR letter issued by the chairman, Sir Edward Knox, shows the present necessitous circumstances of this hospital. Apart from a debt of £1749 owing on the building account of the nurses home, the income of the hospital fell short of the expenditure by £317 in the year 1897, by £636 in 1898, and by £1150 in 1899, showing on the 31st December, 1899, a deficiency of £3852 on the Hospital account as a whole or of £2103 on the ordinary working account.

Correspondence.

INSTITUTIONAL NEUROSIS AND ABORIGINES.

SIR: The description by Richard Asher of institutional neuroses in a recent article in the *British Medical Journal* (April 2, 1960, page 989) attracted my attention. Asher describes this disease as a syndrome of submissiveness, isolation, loss of individuality, automaton-like rigidity and loss of all initiative, which occurs in people who have been in institutions for a long while. According to Asher, this dreadful thing is caused by institutional life and nothing more, and is not confined to mental hospitals, but is found all over the world in orphanages, prisons, convents, homes for displaced persons, prisoner-of-war camps and the chronic wards of municipal hospitals.

The article attracted my attention, because I am interested in the problem of the aborigines in Australia.

In the "Annual Report of the Northern Territory in 1957/58", the folowing figures appear: aboriginal population resident on Government settlements, 3113; aboriginal population resident on mission stations, 4746; total aboriginal population of the Northern Territory, 16,297. The figures of 3113 and 4746 do not include an additional 2377 who are in contact with these institutions; nor does it include 157 at the East Arm Leprosarium. From these figures it is seen that approximately 48% of the full aboriginal population of the Northern Territory is resident in institutions. Why should this be so? They are not orphans, criminals, prisoners-of-war or mentally sick. The answer apparently is because they have a black skin.

The origin of these institutions dates back to our policy of segregating the aborigines. In the early days of settlement the policy was one of exterminating the natives; this was followed by segregation.

[1] From the original in the Mitchell Library, Sydney.

The averred policy of the Federal Government on the aborigines is now that of assimilation. If this is the case, why must these institutions, which are a relic of the days of segregation, persist? The reason in my opinion why they do persist is because they form the basis of a Government-subsidized labour force for the big pastoralists. My reasons for stating this are: (i) The wages of the aborigines are fixed at a lower rate than for whites. (ii) Pastoral work is notoriously seasonal, and the aborigines, when unemployed, receive accommodation, food and clothing at Government expense during slack times. (iii) The aborigines, not having full citizenship and suffering from institutional neuroses, form a submissive labour force and are "resigned" to their low wages. (iv) The institutions care for the dependants of these aborigines, whereas the squatter should be paying higher wages so the aborigines can care for them themselves.

There is a danger inherent in the existence of special Government departments, church missions or other organizations to deal with any dependent persons against whom there are legal discriminations, and who do not enjoy the same legal and political protection as the rest of the population. The very function these bodies perform should progressively render them superfluous. They can claim success in the same ratio as the need for their existence diminishes. Unfortunately they are not rendering themselves superfluous. In fact, they appear to be self-perpetuating and breeding grounds for institutional neuroses.

Yours, etc.,

366 Church Street,
Richmond,
Victoria.
June 25, 1960.

BARRY E. CHRISTOPHERS.

A REPORT ON 500 CASES OF BLEEDING PEPTIC ULCER TREATED MEDICALLY WITH MINIMAL TRANSFUSION OF BLOOD.

SIR: The article in the Journal of June 11, 1960, by W. K. Manning and K. O'Connor, on the subject of bleeding peptic ulcer, is interesting and stimulating, and provides food for thought. One's impression is that this all-medical method of treatment is one which is not widely practised, and this makes a careful appraisal of the premises and the effectiveness of such management, producing what appear to be, on the surface, good results, even more desirable. The mortality rate is very low, but it is noted that this is partly due to case selection.

The exclusion of pulse and blood pressure charts, as an index of progress in a bleeding patient, is rather surprising. It is noted that emergency transfusion of blood was considered necessary in only 13 out of 500 cases, and it is by no means clear from the paragraph on indications for transfusions how clinicians, perhaps not so intimately experienced in the immediate supervision of such patients, can decide when recurrent bleeding is "likely to reduce the hæmoglobin value blow three or four grammes per 100 ml.", or when signs of shock persist "much longer than an hour after apparent cessation of a bleeding episode in a patient resting in bed".

It is noted that three patients of the 500 suffered hemiplegia during treatment, presumably from vascular thrombosis. No mention is made of the occurrence of cerebral thromboses of lesser degree, or of thromboses in other sites such as the coronary vessels. One's impression is that hypotension does in fact predispose to vascular thrombosis in elderly people, and theoretically this should be more likely in patients whose whole system is doing its utmost physiologically to marshal its "thrombosing" resources. Perhaps, then, in the process of selection of cases for this paper, some cases may have been excluded because of the fact that the major factor in death was a complicating vascular thrombosis?

Further information, therefore, is desirable from the authors on these and other points. What, for instance, are the criteria of diagnosis of ulcer, and at what stage was this diagnosis clinched? In what proportion of all cases of gastro-duodenal hæmorrhage treated over the period concerned was proven ulcer the cause of bleeding? What was the percentage of patients dying from bleeding from peptic ulcer who were excluded from the series because the major cause of death was considered to be some condition other than the bleeding ulcer?

Finally, no mention is made of intravenous fluid and electrolyte therapy. Does this mean that fluid balance was satisfactorily maintained by the oral route alone in all cases, in some of which presumably vomiting was occurring?

It is to be hoped that Dr. Manning and Dr. O'Connor will see fit to reply in detail. Their contribution is an important one, and should receive careful consideration, particularly by those physicians and surgeons who have to make the decision as to the necessity for and the timing of operative intervention.

Yours, etc.,

Clark-Hiskens Medical Centre,
Erin Street,
Richmond,
Victoria.
July 7, 1960.

F. J. GRAY.

GENERAL PHARMACEUTICAL BENEFITS.

SIR: After 39 years in general practice, one reads with interest the various comments on the above amendments, as published in your valuable Journal from week to week.

My own comments, which appeared in your issue of December 12, 1959, hinted at further amendments, and stressed the necessity for the medical profession to keep up with the times. Taken in conjunction with the monograph published on June 12, 1955, "The Changing Face of Medical Practice: Retrospect and Prospects", it would appear high time the B.M.A. took another look at the changing face of medical practice, and drew up its own blueprint of what is considered the plan for medical practice in 1960 and onwards.

There is a widespread opinion abroad amongst the medical profession that nationalized medicine is just around the corner, an opinion which I share, after careful scrutiny of the progressive enactments which emanate from high places from time to time.

It was the absence of any plan which enabled the Federal Government to graft the P.M.S. with amendments on to us, with subsequent grumbles, but no really effective alternative. We now see the spectacle of private practice gradually being whittled away by the P.M.S. the P.B.A. and the growth of the medical benefits Societies as envisaged in that monograph.

The obvious answer to the whole situation as we now see it is a scheme of contributory national insurance, embracing doctors, hospitals, chemists, dentists and undertakers. Unless we work out our own plan, we will have a form of socialized medicine foisted on us as they have in Great Britain and New Zealand.

May I quote again Dr Menninger, the eminent New York psychiatrist, from his book "Love against Hate": "By the use of our intelligence and our knowledge we can use the slave of science for the promotion of human happiness. Speed the Day."

It would appear that waving our hands in protest is completely futile, and our best bet is to evolve something acceptable to the Australian economy, in advance of public opinion, and then use our power for the good of the community, and to preserve that fragment of freedom in medical practice which we all, I hope, hold so dear.

Yours, etc.,

H. T. ILLINGWORTH.

17 Boulder Street,
Kalgoorlie,
Western Australia.
June 29, 1960.

SIR: I would like to put on record some minor dispensing difficulties which have beset me since March 1.

While using "Avil" tablets before March, I am now forced to use "Anthisan" as a 5s. anti-histamine. All this is very nice, but why were "Avil" tablets excluded from the list?

A general tonic mixture, such as glycerophosphates combined with vitamins and phenobarb, is much favoured by many practitioners. Such, in liquid or tablet form, is well known under various proprietary names, but this is not permitted for 5s. This combination of drugs is as valuable for adults under psycho-somatic stress as it is for underweight children with nervous coughs which disturb their sleep. Why, please, may I not use one of these preparations for 5s.?

Again, for children, a pleasantly-flavoured sulphaguanidine mixture is not to be found in the prescriber's list. Why?

If every doctor had been circularized and asked to write down his dozen most useful prescriptions, then the authorities would have had a useful basis for a workable and modern prescriber's list.

As it is, I am totally ignorant about some of the drugs mentioned, while others bring back nostalgic memories of the prescriptions we used to write in the 1920's.

Yours, etc.,

S. C. S. COOKE.

Carnarvon,
Western Australia.
July 7, 1960.

DIFFERENCES IN AXILLARY TEMPERATURE DURING GALL-BLADDER COLIC.

SIR: An accidental observation induced the author to record bilateral axillary temperatures regularly during gall-bladder colics.

Fifty observed cases gave noteworthy results. In 11 cases of severe gall-bladder colic there was a definite difference in every case, 2·3° F. (1·3° C.) being the maximum. Out of 18 patients with colic of medium severity there were definite differences in 13 cases, whereas only three out of 21 mild cases have shown any difference.

Only differences of greater than 0·5° F. (0·3° C.) were considered as significant. The higher temperature was recorded in the right axilla in all but three cases, and in these latter, the pain was also found to radiate to the left. The temperature differences disappeared a few hours after the colic subsided.

The mechanism is not known with certainty, but it appears that hyperæmia in the corresponding head-zone plays a part. The author has not found any record of similar observations in the literature. Neither was he able to find differences in axillary temperatures during abdominal colic due to other causes.

These observations have already been published in *Medical Weekly*, Budapest, in 1939, Number 7, in *Medizinische Klinik*, 1940, Number 30, and in *Praxis* (Switzerland), 1942, Number 11.

Yours, etc.,

ALBERT A. DAX.

Goodooga,
New South Wales.
June 28, 1960.

SALES PROMOTION METHODS.

SIR: D.H.A. (N.S.W.) Pty. Ltd.'s newsletter to chemists "Items of Interest', June 14, 1960, Vol. 76, No. 10, features a front-page article: "Arthritis and Common Sense by Dan Dale Alexander, Ph.D." It repeats this gentleman's publicity blurb approvingly: "to discover his inexpensive and successful way to relieve arthritis, D.D.A. studied the disease for over 15 years . . . his visit, together with the publicity . . . should bring about an increase in demand for . . . D.H.A. Finest Cod Liver Oil". I feel that no drug house should use this type of sales promotion.

Yours, etc.,

R. KLUGMAN.

26 Fraser Street,
Homebush, N.S.W.
June 18, 1960.

PREANÆSTHETIC SEDATION FOR CHILDREN.

SIR: I was perturbed to read in the Journal of June 25, 1960, that Dr. Cornish and Dr. Galbraith use a 5% solution of "Pentothal" for induction of anæsthesia in children. Such solutions of thiopentone are no longer considered safe, and their use has been abandoned in most centres.

The weaker 2·5% solution is most suitable for every type of patient. There is no doubt at all that it should always be used for the very young. Numerous papers have been published on the dangers associated with the use of the stronger solution of thiopentone and I do not propose to discuss them again. It should, however, be stressed once more, that accidental intraarterial injection of 5% thiopentone, a danger not altogether prevented by using the dorsum of the hand, has led in the past to gangrene and amputation of the limb.

Now that the new ampoule presentation of thiopentone containing 0·5 gramme of the drug, accompanied by a 20 ml. ampoule of water, is available, I see no reason for using other than the 2·5% solution.

Yours, etc.,

J. G. LOMAZ,
Director of Anæsthesia.

Royal Alexandra Hospital for Children,
Camperdown,
New South Wales.
June 27, 1960.

IT HAPPENED ONE NIGHT.

SIR: "Once again the lone voice is heard in the wilderness'—the wilderness of allergy.

Allergists in Australia, in their attempt to help the unfortunate victims of the many manifestations of allergy, are working in a wilderness of problems and unexplained observations, due to lack of local research. It is in this regard that we welcome any work or observations which may be helpful in fitting any piece into the great jigsaw of allergy.

I would commend Dr. Ion Morrison for sparing some of his time and for his useful observations on "temperature inversion". I would also thank Dr. Clive Sands for his work on "The South-West Wind" and his helpful observations in THE MEDICAL JOURNAL OF AUSTRALIA, June 25, 1960 (correspondence). These are useful contributions to our knowledge.

We are all aware of the "almost epidemic outbreaks" of asthma, hay fever, urticaria, etc., at times — sometimes apparently explainable on the results of work done overseas, but at times apparently quite unexplainable.

We suffer in Australia from the lack of local research, and it is not to our credit that a group of diseases causing suffering to such a large number of our people is not the subject of some organized research. The clinician in this field is hard pressed to find time for any research. I therefore welcome any work which may stimulate thought and possible further investigation, and this is surely what Dr. Ion Morrison has done.

I also welcome Dr. S. K. Rogers' interest and questions in THE MEDICAL JOURNAL OF AUSTRALIA, June 25, 1960. But, Gentlemen, while as medical scientists we should make our criticisms, I feel they should be scientific and constructive where possible, and I would deprecate any degeneration to sarcasm.

Yours, etc.,

DOUGLAS O. CROSS.

217 Macquarie Street,
Sydney.
July 1, 1960.

Notes and News.

Professional Provident Fund.

The following statement on the Professional Provident Fund has been forwarded by Dr. A. R. McCay, Chairman of the trustees.

Because of the many members who are medical practitioners, both Victorian and interstate, and who were unable to attend the first annual general meeting of the Professional Provident Fund on June 23 last, it seems desirable that some account of the first year s operations should be published for their information. Additionally, there may be many who are not members and who are not fully conscious of the many advantages to be gained from this method of providing for retirement. They also may be interested in some account of the progress made.

It is of interest to note that it had been conservatively estimated that in the first year the fund would probably have 180 members and funds in the vicinity of £25,000. It is gratifying, therefore, to be able to report that at April 30 last, when the Fund's financial year closed, there were 340 members, the Fund totalled £100,181 9s. 11d., and temporary reducing life assurance cover to the extent of £1,250,000 had been taken out.

This membership is made up of other professions beside the dental and medical professions, and the classification of age groups and the percentage of each in the fund is of interest (Table I).

The low percentage in the under 30 years group seems to indicate a lack of appreciation by the younger man of the advantage of joining the fund early. Conversely, there is no doubt in the minds of elder members, many of whom have expressed regret that such an opportunity as this was not available to them in the early days of their professional careers.

TABLE I.

Age Group. (Years.)	Percentage
Under 30	10·6
31 to 35	26·7
36 to 40	22·4
41 to 45	15·3
46 to 50	9·7
51 to 55	8·6
56 to 60	5·0
60 and over.. ..	1·7

The accounts as certified by the auditors indicate that during the period under review income totalled £1514 11s. 5d.; however, it should be borne in mind that a large proportion of the contributions have been in the Fund for only a short period. For example, over 40% of the total contributions in the Fund were received during the last two months of the Fund year just ended. In the case of many of the investments held, dividends (or interest) have not become payable since the investments were acquired, and with other investments held, a full year's income had not been received in the initial period ending April 30, 1960.

The accounts show an investments fluctuation of £3,846 19s. 3d. which represents the excess of market value as at April 30, 1960, over the cost price of investments in the Fund. This is, of course, very pleasing, and whilst it is a result of the trustees' policy of investment with capital gains in view, it is also to some extent a reflection of the current trend in values of the better class investments, with the policy of keeping a desirable balance as between the various classes of investment. These have been made in a wide range of securities, including semi-Government stock, deposits, notes, debentures, and preference and ordinary shares. It will be found that as the fund progresses, the results of the Trustees' investment policy will become more marked.

At April 30, the percentage of each class of investment held (on a basis of market valuation) was as follows (Table II):

TABLE II.

Class of Investment.	Percentage.
Ordinary shares	41·34
Preference shares	0·86
Debentures, stocks and notes	29·10
Semi-Government stocks	6·66
Cash (on deposit and at bank since invested)	22·04
Total	100·0

It has always been maintained that the low operating costs were a great advantage which this fund enjoyed over others. The rates charged by the Equity Trustee Company, and the fact that the trustees work in an honorary capacity, have made this possible, and the year's accounts have indicated that these costs were within the limits anticipated.

There has been much argument for and against funds of this type; but the results of the first year's operations are a clear indication of what may be achieved, and certainly augur well for the future.

In conclusion, let it be said that the fund has received gratifying support, and the trustees feel that they can be reasonably well satisfied with the progress made.

Retirement of Professor Lorimer Dods.

It is announced by the Commonwealth Minister for Health, Dr. the Honourable D. A. Cameron, that Professor Lorimer Dods will retire from his dual post of Director of the Institute of Child Health, Sydney, and Professor of Child Health at the University of Sydney, on July 14, 1960. Professor Dods became the first Director of the Institute of Child Health when it was established 10 years ago. His appointment coincided with the creation of the first chair of Child Health at an Australian university at Sydney. Dr. Cameron said the success of the Institute of Child Health as a teaching and research institution and the personal influence of Professor Dods had been the main factors in the establishment of chairs of child health in the medical schools of all other Australian universities. As leader of the Institute's staff of doctors and other specialists, Professor Dods had made a number of contributions to child health. He had taken a leading part in the formation of the Australian Pædiatric Association, inaugurated 10 years previously, and played an active role in the work of the New South Wales Society for Crippled Children, as its principal medical adviser. He had also assisted, with characteristic energy, to develop the machinery for the establishment of the Children's Medical Research Foundation.

Appointment to the Institute of Child Health, Sydney, and the Department of Child Health, University of Sydney.

The Commonwealth Minister for Health, Dr. the Honourable D. A. Cameron, has announced the appointment of Dr. Thomas Stapleton to the positions of Director of the Institute of Child Health, Sydney, and Professor of Child Health in the University of Sydney. Dr. Stapleton holds the degrees of master of arts and doctor of medicine, and is a Member of the Royal College of Physicians. He was Assistant Director of the Pædiatric Unit of St. Mary's Hospital Medical School, London, up till the time of his present appointment. He was also honorary consultant physician of the Paddington Green Children's Hospital, London, and was recently appointed a special justice to sit on the bench of the Children's Court, London. Dr. Stapleton left London in May, 1960, and on his way to Australia stayed at Bonn as a visiting professor for the summer term, giving a special course of lectures on the diseases of children. He had previously worked extensively in England, America and Europe, making special studies of the emotional problems of children and those associated with delinquency. He served with the Royal Army Medical Corps in France, India and the Middle East from 1944 to 1946.

Fifth International Congress on Nutrition.

The Fifth International Congress on Nutrition, to be held on September 1 to 7, 1960, at Washington, D.C., is being arranged under the auspices of the International Union of Nutritional Sciences. One of the main features of the scientific programme will be an all-day symposium on "World Food Needs and Food Resources". The remainder of the programme will consist of seven half-day panel discussions by invited participants, and special sessions of ten-minute papers reporting unpublished original research. Major problems of nutrition throughout the world will be reported and discussed during the meetings. The Organizing Committee of the Congress, under the chairmanship of Dr. Paul György, Professor of Pediatrics at the University of Pennsylvania, is cooperating with American universities and research centres, which will offer lectureship appointments to some of the scientists from other countries who attend the Congress. Further information relating to the Congress may be obtained from the General Secretary, Dr. Milton O. Lee, at 9650 Wisconsin Avenue, Washington 14, D.C., U.S.A.

First International Congress of Histochemistry and Cytochemistry.

The First International Congress of Histochemistry and Cytochemistry will be held in Paris from August 28 to September 3, 1960. The Congress is being organized under the auspices of the *Société française d'histochimie*, in collaboration with histochemical societies all over the world. The President of the Congress will be Professor Jean Verne (France), and histochemists from many countries will be present. Amongst the topics on the provisional programme are "Physical Problems", "Biochemical Data Applied to Histochemistry" and "Applied Histochemistry". Further information relating to the Congress may be obtained on application to the Secretary-General, Dr. R. Wegmann, at 45, rue des Saints-Pères, Paris, VI^e^, France.

Medical Practice.

NATIONAL HEALTH ACT.

THE following notice is published in the *Commonwealth of Australia Gazette*, No. 43, of June 16, 1960.

NATIONAL HEALTH ACT 1953-1959.

Notice in Pursuance of Section 134A.

Notice is hereby given that the Medical Services Committee of Inquiry for the State of Queensland, after investigation, having reported on the nineteenth day of April, 1960, concerning the conduct of Roger William Percy, of Mainroad, Edmonton, a medical practitioner, in relation to his provision of medical services under part IV. of the National Health Act 1953-1959, I, Donald Alastair Cameron, Minister of State for Health, did on the seventeenth day of May, 1960, reprimand the said Roger William Percy.

Dated this seventeenth day of May, 1960.

DONALD A. CAMERON,
Minister of State for Health.

The following notice is published in the *Commonwealth of Australia Gazette*, No. 46, of June 23, 1960.

NATIONAL HEALTH ACT 1953-1959.

Notice under Section 134A.

Notice is hereby given that the Medical Services Committee of Inquiry for the State of New South Wales, after investigation, having reported on 10th November, 1959, concerning the conduct of James Patrick Dermott O'Higgins, of 87 Dalhousie-street, Haberfield, medical practitioner, in relation to his authority under Section 88 of the National Health Act 1953-1959, I Donald Alistair Cameron, the Minister of State for Health, did on the thirty-first day of May, 1960, reprimand the said James Patrick Dermott O'Higgins.

Dated this thirty-first day of May, 1960.

DONALD A. CAMERON,
Minister of State for Health.

Post-Graduate Work.

ST. VINCENT'S HOSPITAL, SYDNEY: GASTRO-ENTEROLOGY UNIT.

A MEETING of the Gastro-Enterology Unit of St. Vincent's Hospital, Sydney, will be held on Thursday, July 28, 1960, at 5.30 p.m. Dr. D. Wightman will speak on "Radiological Investigation of the Biliary Tract". All medical practitioners are invited to be present.

THE WOMEN'S HOSPITAL, CROWN STREET, SYDNEY.

Visit of Professor Howard Taylor.

PROFESSOR HOWARD TAYLOR, Professor of Obstetrics and Gynæcology, Columbia University, New York, will be Guest Professor at the Women's Hospital, Crown Street, Sydney, from Monday, August 22, to Friday, August 26, inclusive. He will spend the mornings at the hospital, taking part in ward rounds, discussion of selected cases and operations. During this week, the seminar will be held on Wednesday, August 24, at 9 a.m. The subject will be "Ante-Partum Hæmorrhage", and the chairman, Professor Howard Taylor. All medical practitioners are invited to attend. A more detailed programme will be announced later.

The World Medical Association.

Pakistan Seeks Eminent Medical Speakers.

THE Pakistan Medical Association has issued a cordial invitation to the member associations of the world to designate representatives of their organization to present papers at the sixth All-Pakistan Medical Conference, to be held in Karachi in November, 1960. The exact dates of

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JUNE 18, 1960.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	2(2)	3(2)	..	..	1	..	..	6
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	4	..	1(1)	..	..	..	6	..	11
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	2(1)	10(9)	1(1)	..	..	4(4)	..	..	17
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	..	..	2	1(1)	..	1	..	4
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	29(13)	29(12)	6(1)	9(2)	5(3)	..	..	..	78
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	1	..	..	..	..	..	1
Malaria	..	1(1)	..	..	..	..	..	..	1
Meningococcal Infection	1	3(2)	..	..	..	..	..	..	4
Ophthalmia	..	..	..	..	1	..	..	..	1
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	1	..	..	..	..	..	..	..	1
Puerperal Fever	..	1(1)	..	..	..	..	..	..	1
Rubella	..	7(6)	..	..	5(3)	..	..	..	12
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	10(1)	17(12)	2	..	1	1	..	..	31
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	14(2)	..	3	..	17
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	13(10)	15(11)	59(14)	3(3)	1(1)	..	1	..	92
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1]Figures in parentheses are those for the metropolitan area.

the Conference will be announced in the near future. The Pakistan Medical Association will provide board and lodging for the medical speakers while they are in Karachi. The names of delegates to the conference and the titles of the papers they wish to present should be addressed as follows: Dr. N. A. Ansari, Secretary, VIth All-Pakistan Conference, PMA House, Garden Road, Karachi 3, Pakistan.

African Goodwill Trip.

A group of Canadians under the auspices of the Canadian Supporting Committee of The World Medical Association, are undertaking an extensive tour of Africa. Among their numerous purposes are: to talk to medical men, discussing common problems and interests, trying to understand their problems and help them see those of the Canadian doctors; and to create and cultivate goodwill and understanding with newly-formed countries such as Ghana, Nigeria, Congo and others.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE following additions and amendments have been made to the Register of Medical Practitioners for New South Wales, in accordance with the provisions of the *Medical Practitioners Act*, 1938-58.

Registered medical practitioner who has complied with the requirements of Section (3) and is registered under Section 17 (1) (a) of the Act: Hodges, Roy John, M.B., B.S., 1956 (Univ. Queensland).

Registered medical practitioners who have complied with the requirements of Section 17 (3) and are registered under Section 17 (1) (b) of the Act: Barr, Ronald Ford, M.B., Ch.B., *1958 (Univ. Glasgow)*; Greenman, Gwen, M.B., B.Ch., 1942 (Univ. Witwatersrand); Iles, David Sidney, M.B., B.S., 1953 (Univ. London); James, Philip, B.M., B.Ch., 1957 (Univ. *Oxford)*; *McCauley*, Henry Robert Bruce, M.B., B.S., 1954 (Univ. London); Miller, Basil James, M.B., Ch.B., 1945 (Univ. Capetown); Mulholland, George Dunseith, M.R.C.S. *(England)*, L.R.C.P. *(London)*, *1952*; *Murray*, James Hastie, L.R.C.P., L.R.C.S. (Edinburgh), L.R.F.P.S. (Glasgow), 1939, D.P.H. (Glasgow), 1947; Witkin, Saul Edgar, M.B., B.Ch., *1952 (Univ. Witwatersrand)*.

Registered medical practitioners who have complied with the requirements of Section 17 (3) and are registered under Section 17 (2) of the Act: Bryer, William Bela, M.D., 1952 (Univ. Budapest); Guastalla, Piero Bruto, M.D., 1936 (Univ. Rome), D.G.O. (Dublin), 1950, L.M. (Rotunda), 1950, M.R.C.O.G., 1953; Seifert, Paul, M.D., 1947 (Univ. Heidelberg).

Notice.

THE CHILDREN'S MEDICAL RESEARCH FOUNDATION OF N.S.W.

THE following is a list of donations to the Children's Medical Research Foundation of New South Wales received from members of the medical profession up to July 8, 1960.

Proceeds of Reunion Dinner of the Sydney University Medical Graduates of 1950, £65 3s. 6d.

Dr. and Mrs. R. I. Furber (further), £41.

Dr. Marjory Thomas, Dr. F. Long, Dr. Hilda Bune, £5 5s.

Dr. W. T. Calov, Dr. M. Henley, £5

Dr. F. J. Kelleher, £2 2s.

Previously acknowledged, £10,238 8s. 4d. Total received to date, £10,372 8s. 10d.

Nominations and Elections.

THE undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association:

Wilson, Henry John Welch, M.B., B.S., 1952 (Univ. London), Central Buildings, Commercial Road, Port Adelaide.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Dainius, Vytautas Peter, M.B., B.S., 1958 (Univ. Adelaide); McKinnon, Donald Campbell, M.B., B.S., 1957 (Univ. Adelaide).

Diary for the Month.

JULY 26.—Tasmanian Branch, B.M.A.: Southern Subdivision.
JULY 26.—New South Wales Branch, B.M.A.: Hospitals Committee.
JULY 27.—Victorian Branch, B.M.A.: Branch Council Meeting.
JULY 28.—South Australian Branch, B.M.A.: Scientific Meeting.
JULY 28.—Tasmanian Branch, B.M.A.: Northern Subdivision.
JULY 28.—New South Wales Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

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